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Pulmonary sarcoidosis: a clinical update

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Abstract

Sarcoidosis remains difficult to diagnose, assess and treat. The last decade has brought significant diagnostic and therapeutic advances in the field of sarcoidosis including endobronchial ultrasound, ^{18}F-fluorodeoxyglucose positron emission tomography and biologics. In this article we use clinical vignettes to discuss commonly encountered cases to illustrate and explain the application of these, and other advances.

Keywords: sarcoidosis, endobronchial ultrasound, positron emission tomography, biologics

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Introduction

Sarcoidosis was originally described by the English physician Jonathan Hutchinson in 1869 as a disorder of the skin.[1] It is now known that sarcoidosis is a multisystem disorder, characterised by granulomatous inflammation for which no other cause has been identified. Diagnosis and treatment of sarcoidosis remain challenging.[2,3] While its aetiology and immunopathogenesis are still poorly understood, the last decade has brought considerable advances in managing sarcoidosis: endobronchial ultrasound (EBUS)-guided lymph node sampling is now routine, and ^{18}F-flurodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scanning is sometimes used in selected cases. Furthermore, although corticosteroids remain a cornerstone treatment, newer 'steroid-sparing' therapies, such as biologics, can be used to treat sarcoidosis.[4] In this evidence-based and practical review, we use clinical vignettes to discuss diagnostic and therapeutic advances and some updates from the recent clinical guidelines.

Search strategy

We based our review on national and international guidelines,[5,6] in addition to searching PubMed and Medline using the terms 'sarcoidosis', 'endobronchial ultrasound', 'positron emission tomography', 'biologics' in various combinations. We also searched publications cited in bibliographies of articles.[4]

Case scenario 1

A 28-year-old non-smoker has an incidental finding of bilateral hilar lymphadenopathy (BHL) on her chest radiograph. A month earlier she presented with malaise, painful ankles and lower limb bruises. She is now asymptomatic, but anxious to know whether she could have cancer. Does she need a bronchoscopy?

Bilateral hilar and right paratracheal lymphadenopathy are common radiographic findings (Figure 1) in asymptomatic sarcoidosis (stage I disease; Box 1). These are often incidental findings and remain undetected until a chest radiograph is performed, usually for another reason. In this case, imaging was appropriately requested based on the classical presentation of sarcoidosis as Löfgren syndrome: erythema nodosum (EN), ankle arthralgia, and constitutional symptoms (malaise, fever, sweating and weight loss) which are associated with BHL.

Box 1 Scadding radiographic staging of sarcoidosis[7]

- Stage I: Lymphadenopathy alone – excellent outcome
- Stage II: Pulmonary infiltrates with lymphadenopathy – progression in 1/3 at 5 years
- Stage III: Pulmonary infiltrates without lymphadenopathy – progression in 2/3 at 5 years
- Stage IV: Pulmonary fibrosis – significant morbidity and mortality

The finding of BHL often results in significant anxiety around the possibility of cancer.[4] While there are many underlying causes of BHL, important differentials include sarcoidosis, tuberculosis and lymphoma (Table 1). Although an absolute diagnosis of sarcoidosis requires a tissue biopsy (demonstrating non-caseating granulomatous inflammation with no alternative causes), a presumptive 'clinical' diagnosis is often appropriate, combined with subsequent review. Biopsy is only required if atypical features such as progressive respiratory symptoms emerge during follow-up.[8]

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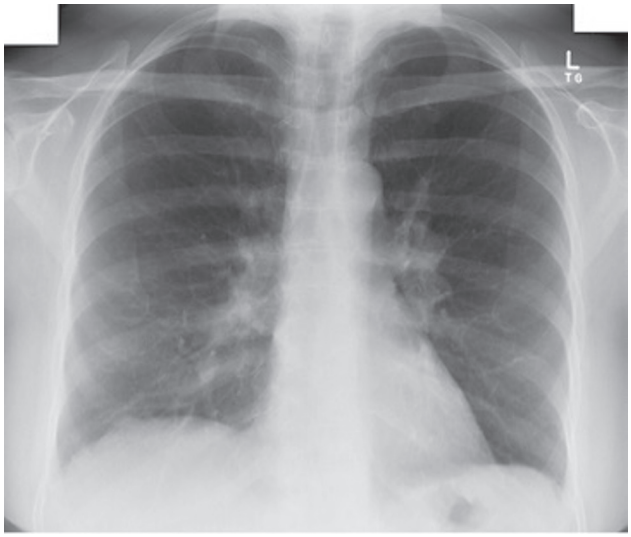
Figure 1 Bilateral hilar lymphadenopathy on a chest radiograph[52]



Clinicians and patients will have their own views as to whether they wish to pursue a tissue diagnosis, and an individualised collaborative pro vs con discussion is recommended. Bronchoscopy under local anaesthetic is usually safe and well tolerated but can be unpleasant for patients. In asymptomatic individuals with BHL, particularly those with EN, sarcoidosis is usually the most likely cause, and a 'wait-and-watch' approach with further chest radiography is acceptable. Nonetheless, some patients may not be entirely reassured and request as much certainty as possible. In these patients a bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be useful and obviate the need for mediastinoscopy.

Outcome

A full history was taken and the patient was completely asymptomatic. There were no features of infection or malignancy. She was on no regular medications, had no family history of lung disease and no relevant exposure to domestic, environmental or occupational dusts. Clinical examination was normal. Blood tests were unremarkable apart from mild lymphopenia, electrocardiogram (ECG) was normal and high-resolution CT (HRCT) scan noted mediastinal and right paratracheal lymphadenopathy, consistent with sarcoidosis, and not typical of lymphoma. No hepatosplenomegaly was seen. Her tuberculin skin test was negative and lung function tests were normal. In view of these findings, she agreed with her clinician that the likelihood of having an alternative diagnosis to sarcoidosis was low. She continued to be reviewed at six-monthly intervals for two years, during which her BHL gradually resolved on chest radiograph, and she was subsequently discharged.

Case scenario 2

A 49-year-old man presents with a two-month history of malaise, cough, breathlessness and 3 kg weight loss. He is a non-smoker with no notable past medical history. Clinical examination is normal, but his chest radiograph and subsequent HRCT are suggestive of stage II pulmonary sarcoidosis. You are keen to make a confident diagnosis – how should he be assessed?

Table 1 Differential diagnosis of bilateral hilar lymphadenopathy (BHL)

Granulomatous	Sarcoidosis
Infections	Tuberculosis, histoplasmosis, coccidioidomycosis.
Malignancy	Lymphoma, carcinoma
Inorganic dust disease	Silicosis, berylliosis
Reactive	Congestive cardiac failure

There is no single diagnostic test for sarcoidosis. Rather, three diagnostic criteria are used:

1. compatible clinical and radiological features
2. compatible histological findings on biopsy
3. exclusion of differential diagnoses

The respective weighting for each criterion will vary with the clinical presentation. For example, Löfgren's syndrome, as in our first case, is a strong predictor of the diagnosis of sarcoidosis with a positive predictive value of 75%, precluding the need for a biopsy in typical cases.[9] Advances are being made in developing diagnostic and prognostic biomarkers for sarcoidosis; however, these are yet to be incorporated into routine clinical practice.[3,10–12]

Initial investigations

A variety of investigations may be decisive in altering the diagnostic probabilities of sarcoidosis:

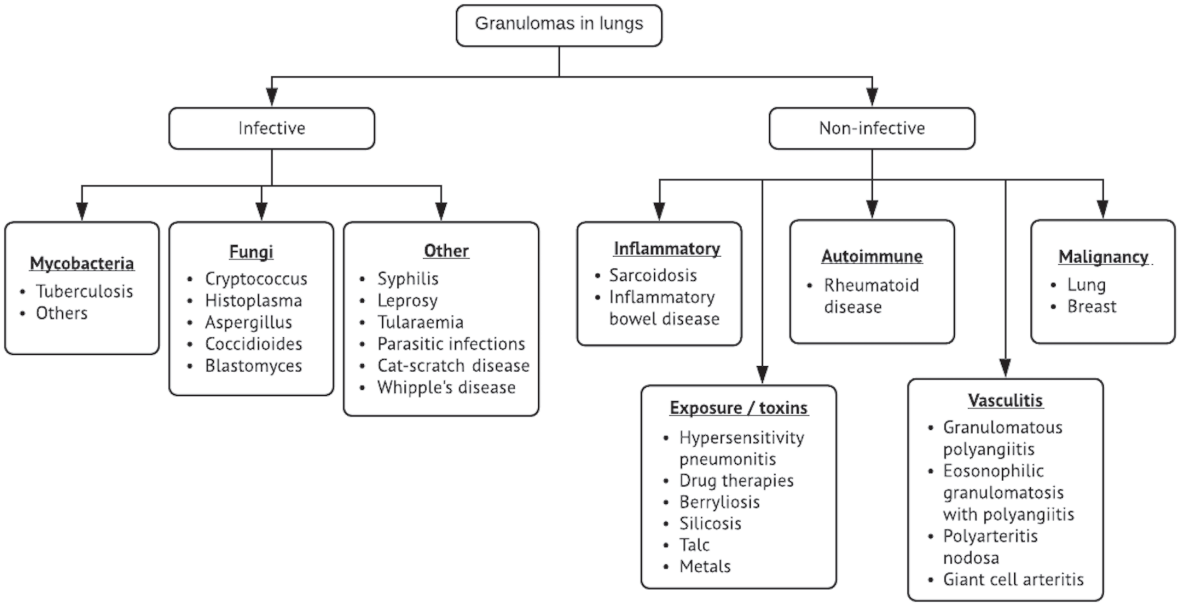
Chest radiography: This is an important initial investigation that should be performed in all patients with suspected sarcoidosis. Around 90% of patients presenting with pulmonary sarcoidosis will have an abnormal chest radiograph.[13]

Blood tests: A full blood count will typically show lymphopenia, since lymphocytes are usually sequestered centrally in the lungs, with relative peripheral depletion in blood. Urea and creatinine, or liver function tests may be deranged in renal or liver involvement, respectively. Macrophage activity in sarcoid granulomas can lead to hypercalcaemia due to altered Vitamin D and calcium metabolism.[14]

Immunoglobulins: Measurement of serum immunoglobulins can differentiate sarcoidosis from common variable immune deficiency, which typically demonstrates hypogammaglobulinaemia and can mimic sarcoidosis with a granulomatous pneumonitis. While rare, this is important not to miss since the management is significantly different.

Human immunodeficiency virus (HIV): HIV infection should always be excluded as both sarcoidosis and HIV can present with interstitial lung shadowing and lymphopenia.

Figure 2 Causes of granulomas in lungs



Serum angiotensin converting enzyme (ACE): This is a controversial test. ACE can be elevated in sarcoidosis but has a diagnostic sensitivity of only 60% and poor specificity – an elevated ACE can be found in many conditions including tuberculosis, hyperthyroidism, alcoholic liver disease, diabetes and lymphoma.[5,15] Furthermore, the concomitant use of an ACE inhibitor reduces ACE levels and genetic polymorphisms can lead to significant inter-individual variability.[16] In 2008 the British Thoracic Society (BTS) suggested routine measurement of serum ACE was not required.[5] However, in 2020 the latest BTS guidelines (in draft format only) suggest ACE should be routinely checked as elevated levels may correlate with disease activity and potentially help during follow-up.[4]

Urine investigations: Urine dipstick, assessing for proteinuria and haematuria, should be performed in all patients with lung infiltrates, to help rule out vasculitides.

Spirometry should be performed in all patients with pulmonary symptoms and an ECG is useful to assess for cardiac involvement. Due to the risk of sight-threatening complications, all patients with suspected sarcoidosis should undergo formal ophthalmological evaluation.[5]

Tuberculin skin test: This test is typically negative in sarcoidosis due to pulmonary sequestration of peripheral T-lymphocytes.[17] A positive test suggests that tuberculosis must be actively excluded.

Imaging

While a chest radiograph can be diagnostic in the appropriate context, HRCT better delineates the extent of disease and potential biopsy sites. Typical HRCT findings include parenchymal nodularity (correlating with granulomas on pathology) along the bronchovascular bundles, interlobular septa and subpleural regions.[18,19] Features of pulmonary fibrosis may be seen in advanced disease and cystic architectural distortion suggests irreversible disease.[20] Notably, sarcoidosis can cause a range of atypical HRCT features which can lead to diagnostic challenges.[21]

Biopsy and bronchoscopy

The pathological hallmark of sarcoidosis is non-caseating granulomas consisting of multinucleated giant cells associated with a chronic lymphocytic infiltrate and varying degrees of fibrosis. Although the diagnosis of sarcoidosis is most secure in the context of a tissue diagnosis, non-caseating granulomas are neither specific nor diagnostic of sarcoidosis as they may be seen in other conditions (Figure 2).[17] This highlights the importance of a thorough clinical assessment and exclusion of other diagnostic possibilities.

The choice of biopsy site is influenced by organ involvement and the ease of access.[22] Skin biopsies are technically easy to perform and sarcoidosis has a predilection for particular sites including tattoos, scars, skin piercings and sites of trauma. EN is not suitable for biopsy because it shows non-specific panniculitis which neither confirms nor refutes the diagnosis. Large extrathoracic lymph nodes can sometimes be easily accessible.[22]

If no peripheral sites are amenable to biopsy, the lungs and mediastinum can be sampled through endobronchial biopsy (EBB), peripheral transbronchial lung biopsy (TBLB), EBUS-TBNA or broncho-alveolar lavage (BAL) (Table 2). While TBLB through flexible bronchoscopy gives access to lung tissue, EBUS-TBNA offers the bronchoscopist the option of 'looking through' the endobronchial mucosa, visualising and sampling lymph nodes that were previously only accessible

Table 2 Application of lung biopsies and needle aspirate in different stages of pulmonary sarcoidosis

Type of biopsy	Utility in pulmonary sarcoidosis
Endobronchial biopsy (EBB)	Endobronchial mucosal involvement
Transbronchial lung biopsy (TBLB)	· Stage II (sensitivity increased with EBUS-TNA) · Stage III · Endobronchial mucosal involvement
Endobronchial ultrasound-guided transbronchial needle aspirate (EBUS-TNA)	· Stage I · Stage II

by mediastinoscopy under general anaesthetic (Figure 3). This technique is both minimally invasive and safe.[23] In one multicentre randomised trial, EBUS-TBNA samples were compared to conventional bronchoscopic biopsies in 304 patients with stage I or II pulmonary sarcoidosis.[24] The diagnostic yield for detecting granulomas was significantly higher in the EBUS-TBNA group. In systematic analyses the pooled yield of EBUS-TBNA ranged from 54 to 93%.[24,25]

BAL is often performed at bronchoscopy and has the advantage of providing cytology and microbiology samples. Although a lymphocytosis with elevated CD4:CD8 T-lymphocyte (>3.5:1) is characteristic of sarcoidosis BAL fluid, this can be normal in 15% of cases.[26,27]

The choice of bronchoscopic investigation will be influenced by pre-test probabilities and degree of pulmonary and extrathoracic involvement.[13] For example, in stage I sarcoidosis, sampling the lymph nodes via EBUS-TNA can have diagnostic yields of around 80% whereas the use of TBLB will have lower yields.[28] In stage II sarcoidosis, TBLB has a 60% sensitivity of detecting granulomas but is associated with complications including haemorrhage and pneumothoraces.[13,26] Here, the diagnostic yield can be increased when EBUS-TBNA is used alongside TBLB. When there is endobronchial mucosal involvement (in around a third of patients), EBB has a yield comparable to TBLB.[29] In patients with stage III sarcoidosis, TBLB has the highest yield.

Outcome

This patient had no skin lesions or extrapulmonary lymph nodes that were accessible to sampling. Blood tests were normal apart from lymphopenia. His lung function was mildly restrictive, with a forced vital capacity (FVC) of 75% predicted. His tuberculin skin test was negative. His HRCT suggested stage II disease and he proceeded to have a flexible bronchoscopy under local anaesthetic with sedation and had EBUS-TBNA with lavage. The EBUS-TBNA samples demonstrated non-caseating granulomatous inflammatory changes and no infection was found on BAL. The patient started a tapering course of oral steroids and remains under review.

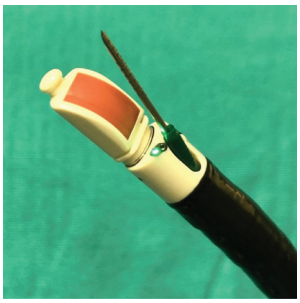


Figure 3 End of bronchoscope showing ultrasound probe and adjacent retractable needle used for lymph node sampling through the airway wall

Case scenario 3

A 49-year-old man with biopsy-proven stage II pulmonary sarcoidosis attends your clinic for further discussion, one week after his bronchoscopy with EBUS. He is keen to know what his prognosis is likely to be.

Sarcoidosis can have a variable clinical course and this uncertainty can contribute to patient morbidity.[30,31] The Scadding classification is still used for staging and prognostication, although imperfect. Individuals with stages III and IV generally have poorer outcomes.[32] Unfortunately, this approach is not personalised and does not allow an accurate assessment of prognosis. Chest radiograph appearances alone do not distinguish between active granulomatous inflammation (and consequent risk of irreversible fibrosis) versus 'burnt out' inactive disease. Furthermore, patients with apparently inactive Stage IV disease may have active disease.[33]

Sarcoidosis is generally not life-limiting. However, in around 8 to 10% of patients a shortened life expectancy is primarily because of pulmonary involvement. In one large cohort study of 452 patients with sarcoidosis, age, extent of pulmonary fibrosis on HRCT and pulmonary hypertension (at right-heart catheterisation) were independent predictors of respiratory mortality.[34] Walsh and colleagues recently developed an integrated prognostic scoring tool for pulmonary sarcoidosis incorporating physiological variables (composite physiological index) and HRCT imaging findings (extent of pulmonary fibrosis and the ratio of pulmonary artery to ascending aorta diameter).[35] When combined, this staging system was strongly predictive of mortality. These models are limited in their ability to prognosticate in the later stages of pulmonary sarcoidosis. There is an urgent need for better prognostic biomarkers, especially in the early stages of disease.

Outcome

Our patient was reassured that while he has some minor fibrotic change on HRCT, this was minimal (10% extent; >20% considered significant) and his FVC was 80% predicted. Furthermore, on his HRCT, pulmonary artery diameter was not increased i.e. similar diameter to his aorta, which together with a normal echocardiogram suggested no significant pulmonary hypertension. He was reassured that he was in a low risk/good prognosis group.

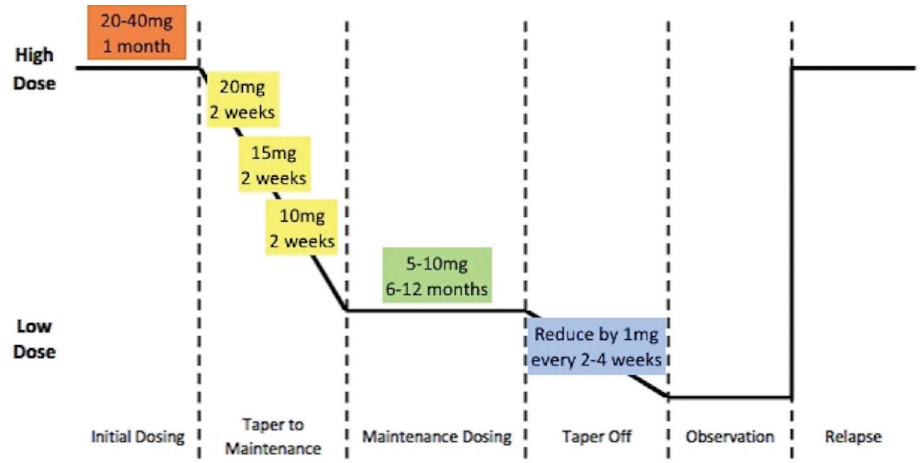


Figure 4 Example of a stepwise approach to initiating and weaning corticosteroids in pulmonary sarcoidosis

Case scenario 4

Your conversation with the same 49-year-old man (in Case 3) with biopsy-proven stage II pulmonary sarcoidosis moves on to treatment options – he wants to know if he needs treatment.

Patients with sarcoidosis may be managed with observation or immunosuppressive medications. The decision to initiate treatment is guided by many factors. Goals of therapy should be established with a risk/benefit dialogue with the patient in the context of likelihood of therapeutic toxicities and spontaneous resolution. Notably, there is poor-quality evidence guiding drug choice, dose and duration. Current guidelines advocate initiating treatment only if there is potential danger of a fatal outcome, permanent disability or an unacceptable loss of quality of life.[4,5] Most patients with stage I and asymptomatic stage II disease do not require treatment, at least initially, as there will be spontaneous resolution of sarcoidosis in as many as 40% of patients. Patients with symptomatic stage II disease, particularly if lung function is impaired, should be considered for drug therapy.

If the agreed decision is to initiate drug treatment, there are three categories available: corticosteroids (mainly prednisolone), immunosuppressants (most commonly methotrexate, azathioprine, leflunomide and mycophenolate) and biologics (mainly infliximab).

First-line treatment

The evidence-base behind the use of corticosteroids in sarcoidosis is limited and the timing of initiation is controversial.[3] For pulmonary sarcoidosis in the absence of life-threatening disease, some clinicians will opt for monotherapy with oral corticosteroids, usually starting with a dose of 20–40 mg of prednisolone for a month, followed by slow tapering to a maintenance dose, usually aiming to reach 5–10 mg once daily (Figure 4). If there is a rapid response then it may be possible to begin weaning towards zero as early as six months. However, in most patients the response is slower, and weaning often begins after 12 months with monitoring for relapses which may necessitate reintroduction of higher doses.

The toxicity risks from prolonged high-dose corticosteroids are considerable, notably obesity, hypertension, osteoporosis and diabetes mellitus.[36] As a general rule of thumb, patients ideally should be on a maintenance dose of <10 mg prednisolone once daily and if they require a higher daily dose, or have relapsed on lower dose corticosteroids, there should be a very low threshold to add in a 'steroid-sparing' immunosuppressants at an early stage, even in the first year.

Second-line treatment

Before adding in another drug, it is important to review the diagnosis of sarcoidosis and discuss compliance with existing therapy. Current guidelines suggest that second-line therapy should be considered if there is:

a. progression of pulmonary disease or an unacceptable symptom burden despite adequate corticosteroids therapy
b. intolerable corticosteroids side effects
c. inability to taper corticosteroids below 10 mg prednisolone once daily
d. the presence of major comorbidities likely to be adversely affected by corticosteroids therapy
e. a strong patient aversion to the use of corticosteroids, in which case a second-line drug may be occasionally used as an initial therapy

The most commonly used drugs are methotrexate, mycophenolate, leflunomide and azathioprine. It is beyond the remit of this article to discuss these drug therapies in detail, but they are described elsewhere.[3] All these drugs have potential for toxicity and therefore should be initiated only after careful thought by clinicians with expertise in their use, with 'shared care' monitoring with primary care partners.

Third-line treatment

Patients who fail second-line therapies should be considered for biologic agents which block the effect of the pro-inflammatory cytokine tumour necrosis factor (TNF), which is important in granulomatous inflammation. These drugs, such as infliximab, are usually given in combination with second-line drugs such as methotrexate. A more detailed

discussion of TNF blockers in sarcoidosis can be found elsewhere.[37] Interestingly, and paradoxically, case reports are now emerging of the development of granulomatous inflammation in some patients treated with biologic immune checkpoint inhibitors used to treat other conditions such as lung cancer (pembrolizumab) and melanoma (ipilimumab).[38]

Outcome

A pro/con discussion was held with this patient regarding observation vs treatment. He understood that it was possible that his sarcoidosis might regress spontaneously, but equally, if his disease progressed with further granulomatous inflammation, he might develop potentially irreversible fibrotic change. He was also advised that corticosteroids would have a useful anti-inflammatory effect in his lungs, but carried potential for toxicity. His preference was for a more conservative initiation dose of 20 mg of prednisolone once daily with a slow taper to 7.5 mg once-daily maintenance. A bone density scan was performed at baseline (normal) and he was specifically counselled about reporting any dyspepsia. He remained well throughout treatment. At nine months, symptoms settled completely and chest radiograph was normal. His corticosteroid dose was therefore weaned by 1 mg each month thereafter, and he had three-monthly clinic reviews with chest radiograph and detailed pulmonary function tests. He managed to wean and discontinue corticosteroids and remains under regular clinic review, mindful of the risk of relapse.

If relapse did occur, we would re-initiate corticosteroids, again with weaning, but would also add in a second-line treatment. Our preference is once-weekly methotrexate with folic acid. The aim is to allow the corticosteroids dose to be gradually weaned, below 10 mg once daily. We tend to continue methotrexate, if tolerated, for a minimum of two years, and then reassess.[39]

Case scenario 5

A 60-year-old female with pulmonary sarcoidosis has been on oral corticosteroids for 18 months and describes profound fatigue, low mood and breathlessness on attempts to wean her prednisolone dose below 10 mg daily. She has gained 9 kg in weight since being on treatment. You are unsure if her sarcoidosis is 'active' or she has become deconditioned. Her chest radiograph notes stage II disease and appears unchanged. Are there tools to help assess disease activity?

This is a common clinical situation. It is possible that she still has inadequately treated pulmonary sarcoidosis, the danger being progressive and irreversible lung fibrosis. Therefore, it may be that she needs additional therapy.[39–42] Equally, it is possible that she has become deconditioned through corticosteroid-associated weight gain and myopathy, and further attempts at corticosteroid weaning should occur. Fatigue and depression are common in patients with sarcoidosis, often not fully acknowledged by treating clinicians, with little high-quality evidence for treatment.[43,44] It is also possible that there are other causes for her symptoms, including unrecognised cardiac sarcoidosis,[45,46] pulmonary hypertension,[47] or sleep apnoea.[48]

Unfortunately, no perfect tool exists to assess sarcoidosis activity. In routine clinical practice it is often estimated by integrating clinical history (symptoms), physiology (trends in lung function such as FVC) and radiology (chest radiograph ± HRCT).[17]

In carefully selected patients, a PET scan can be considered, using 18F-FDG which has high uptake in inflammatory disorders and malignant lesions.[49] PET appears especially helpful in those persistently symptomatic patients without serological signs of inflammatory activity, in patients with radiological signs of fibrosis and in the detection of active cardiac sarcoidosis. PET is also sometimes used to uncover a suitable location for biopsy to obtain histological evidence for the diagnosis and explain extrathoracic symptoms.[49–51]

Suggested strategy

1. Full assessment as discussed in Case 2. In addition, thyroid function tests will exclude hypothyroidism and the possibility of cardiac involvement/pulmonary hypertension should be considered (ECG, echocardiogram and, if ongoing concern, cardiac magnetic resonance imaging).
2. Sleep assessment: Epworth Sleepiness Scale Questionnaire and overnight sleep study – obstructive sleep apnoea is common in sarcoidosis and this patient's increased weight is a predisposing risk factor.
3. PET: as discussed earlier, definitely not a first-line test, but may be useful in carefully selected patients.

Outcome

Blood tests were normal apart from mild lymphopenia. There was no evidence of cardiac disease or pulmonary hypertension on ECG and echocardiogram. A sleep study was normal. Her PET scan, however, noted florid pulmonary parenchymal uptake of FDG (Figure 5), without evidence of abnormal cardiac FDG uptake. Her sarcoidosis was therefore assumed to be still active and she was started on once-weekly methotrexate and folic acid. After three months her corticosteroid was gradually weaned to 5 mg once daily and by six months had been stopped. She regained her pre-diagnosis weight, was seen by a physiotherapist, and enrolled in pulmonary rehabilitation classes, which reduced fatigue. Methotrexate was discontinued after two years following a second PET scan at that time noting no ongoing activity.

Conclusion

There have been major advances in the management of sarcoidosis during the last decade. Nonetheless, many aspects of care remain challenging, and in our review we have used clinical vignettes to explore these further. Key learning points include:

Figure 5a Cross sectional chest imaging (^{18}F-FDG PET CT scan) demonstrating increased uptake of glucose (yellow and red areas in both lungs) consistent with active pulmonary sarcoidosis.

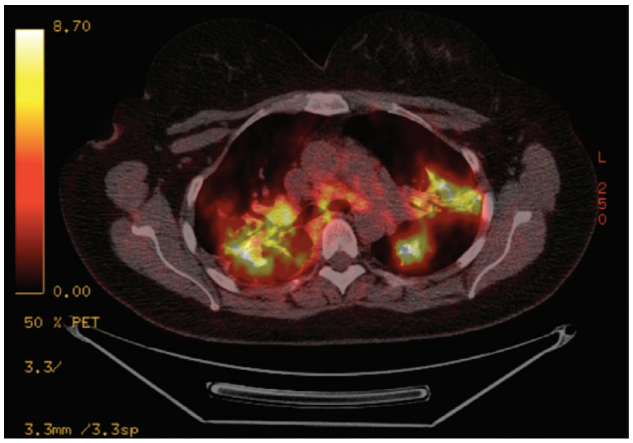
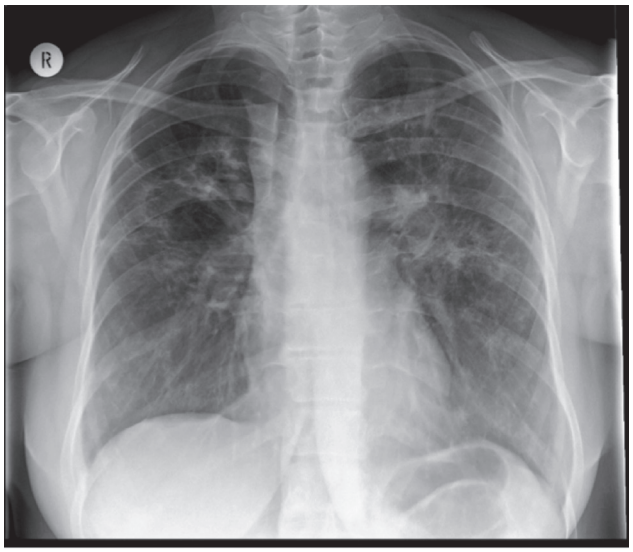


Figure 5b Chest radiograph of the same patient noting stable interstitial lung shadowing – it was unclear without the PET CT scan if the patient's sarcoidosis was still 'active' and required ongoing treatment.



- A diagnosis of sarcoidosis can be made without a biopsy in the context of an appropriate clinical history and chest imaging.
- EBUS-TNA is now routinely used for bronchoscopic sampling in patients with suspected sarcoidosis. It gives access to lymph nodes that were previously only accessible by mediastinoscopy.
- Steroid-sparing therapies, such as methotrexate, should be considered early in patients at risk of corticosteroid-induced toxicities.
- ^{18}F-FDG PET scans can be useful in carefully selected patients to help distinguish active pulmonary sarcoidosis from other differential diagnoses.

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52 Case courtesy of Associate Prof Craig Hacking, Radiopaedia.org, rID: 71482.