Sarcoidosis

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Introduction

The cutaneous lesions of sarcoidosis were first recognised and described by Jonathan Hutchinson in London in 1869 and by Caesar Boeck in Norway in 1899. It is now clear that sarcoidosis affects the lungs in over 90% of cases, and accounts for around a third of the patients with interstitial lung disease (ILD) seen in specialist respiratory clinics. Although the twenty-first century has given us a better appreciation of potential predisposing environmental and genetic factors, the pathogenesis and optimal management of this multisystem condition remain poorly understood.

A significant proportion of patients with active disease are limited in their daytime activities by breathlessness, fatigue, or arthralgia. The course of sarcoidosis varies considerably. While there is a high rate of spontaneous remission, the disease may persist in up to one-third. It is currently not possible to predict with certainty which patients will develop chronic or progressive disease, or how best to manage them.

Treatment is indicated for vital organ involvement and usually consists of systemic corticosteroids with or without other immunosuppressive agents. Biologic drugs such as infliximab may be of value in some patients. Supplemental oxygen may be required. Lung transplantation is reserved for those with respiratory failure who fail to respond to maximal therapy, and is limited by organ availability. Other potential serious complications include pulmonary hypertension, lung cavitation with mycetoma formation, and opportunistic infections resulting from immunosuppression.

Epidemiology

Sarcoidosis is recognised worldwide and affects all racial and ethnic groups. It can present at any age, with a peak incidence between the ages of 20 and 50 years. Variations in incidence around the world probably reflect different environmental exposures, reporting methods, predisposing HLA alleles, and genetic factors. The highest annual incidence of 5–40 cases per 100,000 is reported in northern Europe, while annual incidence in Japan is just 1–2 per 100,000. The condition is much more prevalent in Afro-Caribbean and black populations. Annual incidence among black Americans is approximately three times that in white Americans, with around 35 cases per 100,000 compared with 11 per 100,000. Afro-Caribbean and black patients are also more likely to develop chronic and potentially fatal disease. The condition is more common in

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S. Hart, M. Greenstone (eds.), *Foundations of Respiratory Medicine*,
https://doi.org/10.1007/978-3-319-94127-1_16

females across all racial and ethnic groups. It has been estimated that around 3000 cases are diagnosed each year in the UK.

Pathogenesis

Seasonal clustering of sarcoidosis, with new cases presenting more frequently in the spring and early summer, is well described. This observation, and the fact that the commonest organs involved are the skin, lungs, and eyes, has led to extensive investigation into possible environmental triggers. A number have been reported, including exposure to tree pollen, wood-burning stoves, insecticides, and moulds. Occupational associations have been noted with naval service, metalworking, and handling of building materials. An increased incidence of sarcoidosis was reported in New York City Fire Department rescue workers involved in the aftermath of the 2001 World Trade Center terrorist attack. Berylliosis may be clinically indistinguishable from sarcoidosis; those at risk include workers in aerospace, electronics, and nuclear industries. A careful occupational history is therefore essential. Studies have reported finding T cells and serum antibodies that recognise mycobacterial antigens in patients with sarcoidosis.

Familial sarcoidosis is well documented, with concordance in monozygotic twins apparently higher than in dizygotic twins. In the North American A Case Control Etiological Sarcoidosis Study (ACCESS), patients with sarcoidosis reported siblings or parents with the disease five times as often as control subjects [1]. Phenotypic features and outcomes do not appear to be concordant in siblings, with the exception of eye and liver involvement.

A number of HLA associations are reported with sarcoidosis, including with class I HLA-B8 antigens, and class II antigens encoded by HLA-DRB1 and DQB1 alleles. Associations with non-HLA candidate genes, such as tumour necrosis factor α (TNF-α), interferon-γ, and chemokine receptors, have not been confirmed. The outcomes of genome-wide scans for loci associated with sarcoidosis appear to vary with the population being studied.

Taking into consideration the above, it is presumed that sarcoidosis results from immune responses to various environmental triggers in genetically susceptible individuals. Epigenetic studies to identify interactions between genetic and environmental factors, for instance specific genetic loci and environmental modifiers, would appear to be essential to define the aetiology more precisely.

Pathology

Although not specific for sarcoidosis, the histological hallmark of the condition is the presence of non-caseating granulomas in affected tissues. The process whereby granulomas are generated is incompletely understood, but exposure to unknown antigen(s) appears to result in acquired cellular immunity, with granuloma formation dependent on interaction between antigen-presenting cells and antigen-specific CD4+ T lymphocytes. Triggering antigen(s) appear to favour accumulation and activation of selective T cell clones. Activated CD4+ cells differentiate into type 1 helper T (Th1) cells, predominantly secreting interleukin-2 (IL-2) and interferon-γ (IFN-γ). They thereby augment TNF-α production by macrophages and amplify the local cellular immune response. Despite extensive local inflammation, peripheral anergy may also develop, manifest as a depressed immune response to the tuberculin skin test (TST).

Granulomas may resolve without adverse sequelae, but pulmonary fibrosis is a complication in up to 25% of patients. The precise causes are unclear, but may reflect a shift to a Th2 cell phenotype with increased production of interleukins 4, 10, and 13. Alveolar macrophages activated in the presence of a Th2 cytokine profile produce increased levels of fibronectin and the CC motif ligand 18 (CCL18) chemokine. CCL18 increases lung fibroblast collagen production, which in turn increases macrophage release of CCL18, perpetuating the development of fibrosis which can result in irreversible damage.

Clinical Presentations

Patients may present in a variety of ways (Fig. 16.1a–j). Good education for healthcare practitioners who may not previously have encountered the condition is thus vital to help prevent delays in referral and diagnosis. Patients may be asymptomatic, and physical examination may be normal. Abnormalities on chest radiograph (CXR) or computed tomography (CT) scanning may be noted as an incidental finding during pre-employment screening or while undergoing investigations for an unrelated condition. Patients may present acutely with the classic Löfgren's syndrome, comprising erythema nodosum, arthritis, and bilateral hilar lymphadenopathy (BHL) on CXR. Alternatively, they may present with a more insidious onset of non-specific symptoms including fatigue, sweats, weight loss, and arthralgia. Cough (usually dry) and breathlessness are frequently reported. Less common but well described is Heerfordt's syndrome, consisting of fever, parotid enlargement, anterior uveitis, and facial nerve palsy.

Other extra-pulmonary symptoms and signs depend on the affected organ(s). Acute uveitis is a potential cause of irreversible blindness, which mandates urgent ophthalmology review and treatment. Patients with cutaneous lesions including erythema nodosum, nodules, and plaques may present to the dermatology clinic; those with arthralgia or dactylitis may be referred to the rheumatology service. Neurosarcoidosis can present acutely with the effects of a space-occupying lesion causing hemiplegia or seizures, or with encephalitis, aseptic meningitis, or isolated nerve palsies. Hypercalcaemia in sarcoidosis results from conversion of 25-hydroxyvitamin D3 to the active 1,25 di-hydroxy-vitamin D3 metabolite by macrophages in sarcoid granulomas. Patients with hypercalcaemia and/or hypercalcuria may present to the emergency unit, endocrinology, or renal clinics. Patients may present to infectious diseases or fever clinics with lymphadenopathy and/or pyrexia of unknown origin, or to the haematology service with anaemia and/or hepatosplenomegaly. Although rare, intrahepatic cholestasis and portal hypertension may prompt initial referral to gastroenterology or hepatology. Ventricular tachycardia is an increasingly recognised presentation of cardiac sarcoidosis; other complications include conduction abnormalities and heart failure.

Patients may thus present not only to respiratory specialists, but to a wide variety of clinicians in other disciplines. The range of organ involvement has important implications for diagnosis and management in individual cases. Optimal management of sarcoidosis therefore frequently requires close working across different specialities. How this is best delivered in any particular unit will depend on local referral patterns, available resources, and service configuration.

As there is no single, specific diagnostic test for sarcoidosis, making the diagnosis requires the clinician to establish a compatible clinical picture, where possible with histology, after excluding other conditions capable of producing a similar clinical or histological picture. A thorough and detailed history is an essential pre-requisite. In suspected sarcoidosis, investigations should be aimed at providing histological confirmation, evaluating the extent and severity of organ involvement, assessing whether the disease is likely to progress, and whether treatment is indicated.

Investigations (see Table 16.1)

Laboratory Evaluation

Initial laboratory investigations include full blood count to look for anaemia and/or lymphopenia; and renal, liver, and bone profile. Liver function tests are abnormal in around 10% of cases, most commonly in Afro-Caribbean and black patients. Liver ultrasound and biopsy may be required subsequently to help confirm the diagnosis. Hypercalcaemia resulting from sarcoidosis is an indication for systemic treatment, but other causes need to be excluded. Urine dipstick is part of the necessary work-up in ILD patients to help exclude vasculitis or nephritis. Twenty-four-hour urinary excretion of calcium should be measured in all patients; intrarenal calcium deposition can lead to renal failure, although renal failure due to granulomatous nephritis is rare.

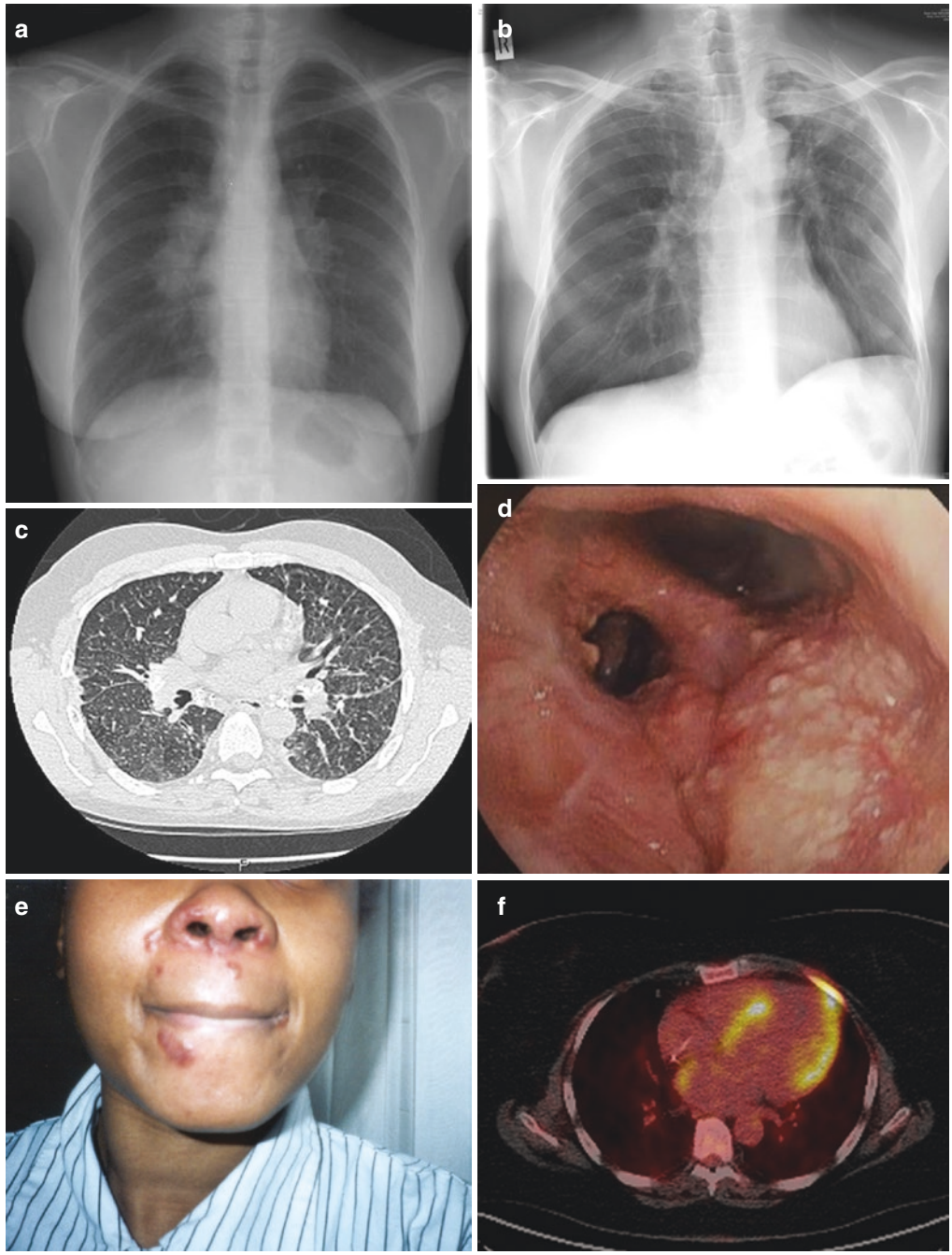

Fig. 16.1 (**a**) Chest X-ray showing bilateral hilar lymphadenopathy. (**b**) Chest X-ray showing bilateral upper lobe fibrosis with left apical mycetoma. (**c**) High-resolution CT scan showing parenchymal nodularity and characteristic beading of the fissures. (**d**) Endobronchial nodularity seen at bronchoscopy (image courtesy of Prof. Martin Walshaw). (**e**) Cutaneous sarcoidosis. (**f**) ^{18}FDG-PET CT axial image showing avid patchy activity in the myocardium. (**g**) ^{18}FDG-PET scan from a patient with sarcoidosis showing extensive lymphadenopathy. Arrows indicate FDG uptake in lymph nodes, spleen and liver. (**h**) Gallium scan showing panda (periorbital and parotid glands) and lambda (mediastinal and hilar nodes) pattern of uptake (image courtesy of Mike Hughes). (**i**) brain MRI (T2-weighted spin echo image) showing signal abnormality in left temporoparietal white matter in a patient with neurosarcoidosis. (**j**) brain MRI (post-gadolinium contrast T1-weighted image) showing focal nodular leptomeningeal contrast enhancement (blue arrowheads) in a patient with neurosarcoidosis (image courtesy of Dr. Chris Rowland-Hill)

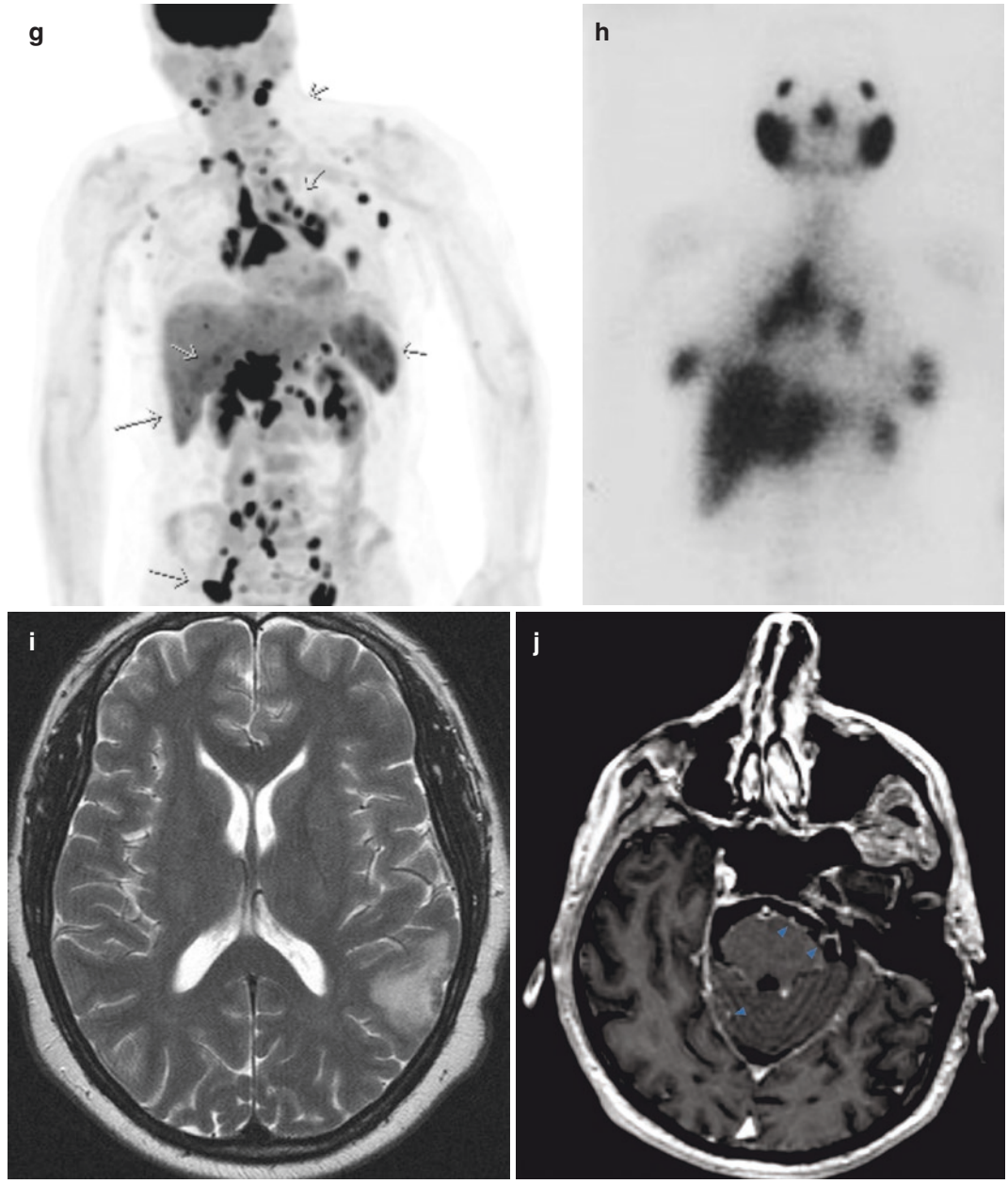

Fig. 16.1 (continued)

Serum angiotensin converting enzyme (ACE) activity levels are raised in up to two-thirds of patients because of excess ACE production by sarcoid granulomas. Although the test lacks sensitivity and specificity, it does reflect granuloma burden. Elevated ACE activity usually falls with treatment and may be a guide to compliance as well as disease activity. A polyclonal increase in immunoglobulins may help to distinguish sarcoidosis from other less frequently encountered granulomatous conditions such as common variable immunodeficiency. Measurements of serum levels of soluble IL-2 receptor have been reported to correlate with disease activity, but are not routinely available in clinical practice.

Table 16.1 Clinical evaluation of patients with suspected sarcoidosis

Initial assessment	Laboratory evaluation	Radiology	Physiology	Biopsy	Further investigations as required for extra-pulmonary disease
History, including occupational or environmental exposures and family history Examination	Full blood count Inflammatory markers: C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) Biochemical profile: Renal function; liver enzymes including alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase; bone profile including serum calcium Serum angiotensin converting enzyme (ACE)* *ACE levels are suppressed and therefore unreliable if the patient is taking an ACE inhibitor Immunoglobulins Urine dipstick 24-h urinary calcium T cell-based blood test and/or skin testing for tuberculosis according to local guidelines	PA chest X-ray High-resolution computed tomography is usually indicated to evaluate the lung parenchyma, except in clear-cut cases of Löfgren's syndrome. It is essential in the following circumstances: • atypical clinical and/or chest X-ray findings, including massive or suspicious lymphadenopathy • suspected bronchiectasis, mycetoma, pulmonary fibrosis or malignancy • normal chest X-ray but clinical suspicion of sarcoidosis	Pulmonary function tests (before bronchoscopy): Spirometry, total lung capacity and diffusion (TLCO/KCO) 12 lead electrocardiogram (ECG)	Bronchial, transbronchial biopsy and/or EBUS-TBNA, or biopsy of an affected extra-pulmonary organ	Fundoscopy and slit-lamp examination Echocardiography Holter monitoring Cardiac PET and/or MRI Right heart catheterisation Brain MRI and lumbar puncture with analysis of cerebrospinal fluid

An important differential diagnosis is tuberculosis (TB). Because of peripheral anergy, the tuberculin skin test (TST) in sarcoidosis patients has a high specificity but poor sensitivity for TB. Thus, although a negative TST in the general population is a feature of sarcoidosis, a positive TST in a patient suspected to have sarcoidosis mandates thorough investigation for TB. Interferon gamma release assays have a higher specificity and sensitivity for detecting TB infection because they employ antigens specific for *Mycobacterium tuberculosis* complex. Current data suggest that their predictive value for TB is good, even in patients with sarcoidosis. They remain positive in many patients and may detect latent TB infection more accurately. Local guidelines should be followed when deciding which investigation(s) to employ to help exclude TB.

Radiology

CXR is essential, and in all but the mildest of cases, such as acute and self-limiting Löfgren's syndrome, high-resolution computed tomography (HRCT) scanning is advisable to examine the lung parenchyma for abnormalities. Scadding's original staging of CXR changes (see below) underestimates the extent of pulmonary involvement when compared with HRCT, but still has prognostic value, with stage 0 conferring the best prognosis and stage IV the least favourable outcome.

Scadding's Chest Radiograph (CXR) Staging in Sarcoidosis [2]

Stage 0	Normal CXR
Stage I	Bilateral hilar lymphadenopathy (BHL) with clear lung fields
Stage II	Hilar lymphadenopathy with interstitial infiltrates[1]
Stage III	Interstitial infiltrates
Stage IV	Pulmonary fibrosis

[1]Typically predominant in the upper zones.

Physiology

Lung function tests (spirometry, lung volumes and diffusion capacity) should be performed to exclude or confirm physiological defects. Normal lung function tests, despite widespread radiographic abnormalities, is a characteristic feature of sarcoidosis. Conversely, there may be significant physiological dysfunction with clear lung fields, for example in endobronchial sarcoidosis. Classically there is restriction with reduced gas transfer, but airflow obstruction is not uncommon, resulting from endobronchial involvement. Routine electrocardiography (ECG) is recommended to exclude obvious conduction defects which may be asymptomatic.

Biopsy

Aside from TB, the other important differential for BHL in younger patients is lymphoma. Bronchoscopy and/or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) should be considered if the radiology is abnormal. Bronchoscopy should include bronchial washings to exclude infection, and bronchoalveolar lavage (BAL) for differential cell count. This typically shows a lymphocytic picture, with neutrophilia in patients with pulmonary fibrosis. Endobronchial biopsies (EBB) yield a diagnosis in around 40% of cases, especially if the mucosa is visibly abnormal. Transbronchial biopsy (TBLB) has an estimated 60% sensitivity for finding granulomas in patients with sarcoidosis, but confers a 2–6% risk of significant haemorrhage and pneumothorax. Studies of a combined transbronchial and endobronchial approach report a positive diagnosis up to 86% of cases. Biopsies should also be sent in saline for culture in order to exclude TB.

Both endoscopic ultrasound (EUS) and EBUS-TBNA have a higher sensitivity for obtaining non-caseating granulomas from affected lymph nodes. EBUS-TBNA is safer than TBLB, conferring only a 1% risk of significant haemorrhage, pneumothorax or other complications. Current data suggest that EBUS-TBNA provides the highest

diagnostic yield, especially when combined with TBLB, but many clinicians prefer to avoid TBLB because of the associated risks. EBUS-TBNA is generally safe and well-tolerated, but procedure time for EBUS-TBNA is significantly longer than for conventional bronchoscopy alone.

Where there is evidence of disease involving other tissues, for instance peripheral lymphadenopathy or skin lesions, these should be considered as less invasive targets for biopsy. Biopsy of erythema nodosum reveals non-specific panniculitis and is not diagnostic.

Further Investigations in Extra-Pulmonary Disease

Echocardiography should be performed if there is concern about possible myocardial sarcoidosis, or in suspected pulmonary hypertension. Symptomatic cardiac sarcoidosis is estimated to occur in around 5% of patients; autopsy studies in North America suggest a prevalence of around 25%. The prevalence of pulmonary hypertension ranges between 5% and 15%. Although more common in stage IV disease, it can also occur with relatively normal lung parenchyma and function. Referral for consideration of right heart catheterisation is important if there is evidence of pulmonary hypertension on echo.

Further investigations in suspected cardiac sarcoidosis include gadolinium-enhanced cardiovascular magnetic resonance (CMR), and referral to cardiology for consideration of myocardial biopsy. However, myocardial biopsy is not highly sensitive because of the patchy nature of the disease, and may not be required if there is positive histology from a non-cardiac site in the presence of a compatible clinical picture [3]. There are no pathognomonic features for sarcoidosis on CMR, but sub-epicardial lesions in the free ventricular wall or interventricular septum that demonstrate late enhancement with gadolinium are suggestive. Correct interpretation requires a cardiologist or radiologist with specific expertise in the condition. Ambulatory electrocardiography (Holter monitoring) may be required for investigation of arrhythmias.

In patients with suspected neurosarcoidosis, gadolinium-enhanced MRI is indicated to look for brain lesions; MRI can also help monitor response to treatment. Lumbar puncture and analysis of cerebrospinal fluid (CSF) should be considered in collaboration with neurology. Lymphocytic inflammation is characteristic; ACE level estimation can be of value as a pointer to the diagnosis despite its limitations. Oligoclonal immunoglobulin bands may be elevated in CSF, and the condition may be difficult to differentiate from multiple sclerosis.

Further investigations which may be helpful in some patients include ^{67}Ga gallium scanning and ^{18}F fluoro-deoxyglucose positron emission tomography (^{18}FDG PET). The basis of gallium scanning is the ability of the active, freely dissolved gallium ion Ga^{3+} to bind to bacterial products, leucocyte lactoferrin, and inflammatory proteins. It is therefore non-specific, highlighting tumours, inflammation, and areas of acute or chronic infection. However, ^{67}Ga scanning in sarcoidosis may reveal classic "lambda" or "panda" patterns of radiotracer uptake, which help support the diagnosis in atypical cases. The technique entails significant radiation exposure and cannot be used sequentially to monitor response to treatment. Gallium scanning has largely been replaced with FDG-PET scanning.

FDG is taken up by metabolically active cells, so that ^{18}FDG PET may also yield false positives in malignancy or other inflammatory conditions. However, it can help to identify potential diagnostic biopsy sites in patients with possible sarcoidosis, and confers a lower radiation dose than gallium scanning. It may also be a valuable alternative to CMR in patients with suspected or proven cardiac sarcoidosis and a non-MRI compatible pacemaker or defibrillator, and may be used to monitor response to treatment. Interpretation of the findings of these nuclear imaging techniques requires a specialist with specific expertise.

The eye is involved in up to 80% of patients with sarcoidosis. All patients with symptomatic, biopsy-proven, or a firm clinical diagnosis of sarcoidosis should have ophthalmology review including slit-lamp examination and fundoscopy.

Treatment

General Strategies

Clear communication to patients regarding diagnosis and management is essential, given the uncertainty in the majority of cases as to the cause of the condition, treatment, and prognosis. Many North American, European, and British professional societies and charities provide high-quality patient information.

Erythema nodosum alone is not an indication for corticosteroid treatment, but can be painful. It is best managed with paracetamol and/or a non-steroidal anti-inflammatory drug.

Smoking cessation advice should be given to all patients. The outcomes of randomised controlled trials of pulmonary rehabilitation in sarcoidosis are awaited. However, patients with sarcoidosis and pulmonary disease causing deconditioning, disabling breathlessness, impaired quality of life, nutritional deficits, fatigue, and social isolation share many features in common with those suffering from chronic obstructive pulmonary disease (COPD), and should be considered for pulmonary rehabilitation.

Fatigue may be troublesome and impact severely on the patient's daily life and employment. Other causes, including depression and hypothyroidism, should be excluded. Corticosteroids are not usually indicated for sarcoidosis-associated fatigue; they may ultimately worsen matters by inducing weight gain, diabetes, and obstructive sleep apnoea. Lifestyle measures, including attention to diet, weight, sleep, and regular exercise, are important. Small case series have shown improvement with the neuro-stimulant methylphenidate, and two small, randomised controlled trials, one of dexmethylphenidate and one of armodafinil, have also reported benefit [4, 5]. These agents are not currently licensed for use in sarcoidosis in the UK.

Gastro-oesophageal reflux should be treated to help limit cough and possibly prevent potential exacerbation of pulmonary fibrosis. Patients with pulmonary disease and/or pulmonary hypertension who fulfil criteria for supplemental oxygen, whether ambulatory or long-term, should be assessed and managed according to national guidelines. Referral for lung transplantation may be appropriate in patients with respiratory failure. Palliative care referral may be necessary in a minority of patients in whom all other forms of treatment have been exhausted. Avoidance of excessive sun exposure is commonly advised, particularly for patients who have suffered from hypercalcaemic or who have hypercalciuria.

Wherever possible, patients with sarcoidosis should be consented for inclusion into appropriate national registries and/or high-quality clinical trials. Only by collecting relevant data can the epidemiology be better understood and service delivery improved; only by prosecuting high-quality research can therapeutic advances be made which will benefit patients with this intriguing condition.

Pharmacological Strategies

Systemic Corticosteroids

There are no clear criteria for initiating corticosteroid therapy for pulmonary disease. Spontaneous remission occurs in up to 90% of patients, and the natural history is variable. The long-term value of corticosteroid treatment remains unclear, and there are important potential adverse effects [6, 7]. Nevertheless, the effectiveness of oral corticosteroids in pulmonary sarcoidosis was first reported in the 1950s, and they have been widely used since the 1960s. An early study showed that a short course of adreno-corticotrophin hormone (ACTH) or cortisone attenuated infiltrates seen on CXR, and that prolonged cortisone treatment induced remission of granulomas in repeat biopsy samples. Subsequent studies have confirmed clinicians' observations of short- to medium-term (weeks to months) symptomatic, radiographic, and functional improvement. Even in patients with chronic disease previously untreated for

several years, oral steroids can be of short-term clinical value.

In contrast, the long-term benefits of oral corticosteroids, and in particular whether they prevent pulmonary fibrosis and/or improve survival, are much less clear, with most studies showing no definite evidence of benefit. The numbers of patients in these studies ranges from under 20 to over 150. Interpretation is complex because of differences in disease phenotype, with some patients showing spontaneous regression and varying degrees of residual scarring, while others develop persistent disease. Significant long-term disability resulting from pulmonary fibrosis is estimated to arise in up to 20% of patients.

Many studies have included patients with stage I disease on CXR. This has cast doubt on the interpretation of the results, because in many of these patients the condition resolves spontaneously without treatment. In most series steroids were started at the time of presentation, whereas in everyday practice most respiratory specialists delay treatment in favour of careful monitoring. Many studies used a treatment protocol which did not include gradual tapering of the dose according to response, although this is also common clinical practice. Ethnic diversity is a further important consideration: most North American studies included a large proportion of black and Afro-Caribbean patients in whom sarcoidosis is often more severe. Their results may therefore not be applicable in white European populations.

The British Thoracic Society (BTS) open-label study attempted to model real-life practice more closely by including a 6 month observation period before starting oral corticosteroid treatment [7]. Patients with no evidence of spontaneous improvement after this time were started on treatment, and alternately allocated to one of two groups. The first group were treated with steroids for at least 18 months (prednisolone 30 mg daily for 1 month, reducing by 5 mg every month to a maintenance dose of 10 mg daily) with the goal of achieving and maintaining maximal radiographic improvement. In the second group, treatment was restricted to those who required symptom relief or who had deteriorating lung function. Patients were followed up for 5 years.

Patients in the prednisolone group showed greater improvements in symptoms, lung function, and radiographic appearances than those in the control group, with an average difference in vital capacity at final review of 9% predicted. Of the 149 subjects recruited, 39% showed spontaneous radiographic resolution after 6 months, and 22% needed steroids for symptoms. Most of the patients in this study were Caucasian. Side effects of treatment were frequent but mostly mild, and led to withdrawal in only two patients.

Symptom relapse on reducing or withdrawing steroids is well-recognised. One retrospective study suggested that relapse occurred more often in patients previously treated with steroids than in those who had experienced spontaneous resolution, raising concern that steroid treatment itself could contribute to disease prolongation. However, most of the patients included in this study were treated for extra-pulmonary disease, most were black or Afro-Caribbean, and those experiencing spontaneous remission had milder disease initially. Current BTS guidelines on pulmonary sarcoidosis conclude that it is unclear whether steroid treatment might have a negative effect on longer-term prognosis.

A systematic review of steroid treatment in pulmonary sarcoidosis endorsed data from just eight studies out of 150. Six studies examined oral steroids alone, one study treated patients with oral steroids followed by inhaled steroids, and the final study examined inhaled steroids alone. The authors concluded that oral corticosteroids improve CXR appearances after 6–24 months of treatment and result in small increases in vital capacity and diffusing capacity. It is not known whether these benefits are maintained after 2 years, and there are no data confirming that steroid treatment influences long-term disease progression. For these reasons, most clinicians agree that oral corticosteroids are not indicated in patients with Stage 0 or Stage I disease unless lung function parameters are declining.

The starting dose of prednisolone in controlled studies has varied from 30 to 60 mg daily, usually

tapering each month according to response, to an average of 10 mg daily. This dose is generally maintained for between 6 and 12 months before attempting slow withdrawal. Anecdotal observations suggest that in some patients, treatment is best continued for at least 2 years to prevent relapses. Alternate-day dosing, with the dose kept equivalent to the average daily dose, may limit side effects and has been shown in at least one controlled study to be as effective as daily treatment. Such a regime should be discussed carefully with patients before deciding whether to implement it. Diabetic patients may prefer daily dosing to maintain consistent blood glucose readings, and others may have greater difficulty remembering to take their treatment if it not prescribed daily.

Patients with life-threatening or severe vital organ involvement, for instance cardiac disease, neurosarcoidosis, or other complicated extra-pulmonary disease, should be managed in collaboration with the appropriate specialist(s). They may be treated initially with pulsed-dose intravenous methylprednisolone. After 3 days, treatment is usually converted to oral prednisolone at a once-daily dose of at least 60 mg.

Steroid treatment guidelines are summarised in Table 16.2. There is agreement that oral corticosteroids should be considered in patients with severe, persistent, or progressively worsening respiratory symptoms, or declining lung function. Severe symptoms are those which interfere with essential aspects of the patient's daily life, such as work or caring for young children. Many physicians monitor lung function (VC and TLCO) for 6 months before deciding that there is progressive deterioration. There are no absolute cut-offs to determine when treatment is necessary,

Table 16.2 Guidelines on steroid therapy for sarcoidosis

	Steroid therapy	Prednisolone dose	Treatment failure
American Thoracic Society (ATS), European Respiratory Society (ERS), World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) joint statement 1999 [17]	Steroids are effective short-term but it is not known whether they alter the natural history of the disease, or for how long treatment should continue. Patients with progressive symptomatic disease, or asymptomatic patients with infiltrates on CXR and progressively worsening lung function, should probably be treated	Initial dose 20–40 mg/day for pulmonary sarcoidosis, or the equivalent taken alternate days Further evaluation of response after 2–3 months. In steroid responders, gradually tapering the dose to 5–10 mg/day (or an equivalent alternate day dose), and treat for at least 12 months	In patients who fail to respond to steroids after 3 months, consider reasons for failure such as the presence of irreversible fibrosis, non-compliance, or inadequate dosage
British Thoracic Society (BTS)	Steroid treatment is not indicated for asymptomatic stage I disease, nor in asymptomatic patients with stage II or III disease with mild lung function abnormalities and stable parameters. Oral corticosteroids are first-line therapy in patients with disease progression (as indicated by radiology or lung function) or significant symptoms	Initial dose 0.5 mg/kg/day for 4 weeks, tapering to a maintenance dose which controls symptoms and disease progression, for a period of 6–24 months	Consider other immunosuppressive agents when corticosteroids are not controlling the disease, or when side-effects are unacceptable. Methotrexate is the second-line agent of choice

but a fall in VC of 10% and/or TLCO of >15% is generally considered significant. There is agreement that neither oral nor inhaled corticosteroids are indicated in asymptomatic patients in the absence of other organ involvement.

Inhaled Corticosteroids

The value of inhaled budesonide was first reported in an open study of 20 patients with pulmonary sarcoidosis. Several subsequent studies have investigated the potential of inhaled steroids, either used first-line or as maintenance treatment, after a response is obtained with oral steroids. Only two studies, both using budesonide, have showed conclusive benefit.

Current evidence suggests that inhaled steroids are less consistently effective than oral steroids in pulmonary sarcoidosis. It is generally agreed that they should not be employed routinely. They may, however, have a role in maintenance treatment, or as steroid-sparing agents; they may also be of value in those patients whose main symptom is a troublesome cough and/or who have evidence of endobronchial involvement.

Alternative Immune-Suppressants

A number of patients with severe or persistent sarcoidosis require treatment with alternative agents, usually in combination with corticosteroids, but sometimes alone. Treatment with an alternative agent may be required for patients in whom corticosteroids are contra-indicated, for those unable to tolerate the side-effects of steroids, for those whose disease is refractory to corticosteroids, or for those who are continuing to require unacceptably high doses. In the absence of clear evidence, such decisions need to be made on a case-by-case basis. It seems reasonable to consider adding a second-line agent if the patient is continuing to require in excess of 10 mg prednisolone once daily after 6 months, and if there is no indication of likely improvement or potential to reduce the dose over the following 6 months.

The range of potential alternative immunosuppressive agents is wide. It includes methotrexate (MTX), azathioprine, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil (MMF), ciclosporin A, and chlorambucil; as well as anti-TNFα agents including pentoxifylline, thalidomide, infliximab, and etanercept. Most of the literature examining these agents consists of small case series, and many have focused on the effects of these agents on extra-pulmonary rather than pulmonary disease. The most commonly used are generally MTX, azathioprine, hydroxychloroquine, and MMF. Limited evidence supports MTX as the second-line drug of choice after corticosteroids. However, there is no clear evidence as to which immunosuppressant should be used thereafter, if prednisolone and/or MTX fail to control the disease.

Methotrexate

MTX has been employed as a steroid-sparing agent for many years in the treatment of rheumatoid arthritis. It is a folic acid analogue which inhibits dihydrofolate reductase and trans-methylation reactions. At low doses it has anti-inflammatory properties, attributable largely to enhanced adenosine release. Adenosine suppresses TNFα release from monocytes, macrophages, and neutrophils; suppresses neutrophil reactive oxygen species release; and inhibits lymphocyte proliferation.

A randomised controlled trial of MTX (10 mg once weekly) or placebo plus oral prednisolone in 24 patients, conducted over 1 year, showed that patients taking MTX required significantly less prednisolone in the second 6-month period. However, the trial was limited by a high drop-out rate, with only 15 patients remaining in the study after 6 months. MTX did not differ from placebo on an intention-to-treat basis, and lung function, radiology, and symptoms did not differ between the two groups.

With the exception of teratogenicity, the most important side effects of MTX are hepatic fibrosis and leucopenia. Baseline liver function should be documented before starting treatment, but abnormal liver function resulting from sarcoidosis is not a contra-indication to MTX. Where appropriate, serology for HIV and hepatitis B and C should be sent before starting treatment. Significant renal disease, and acute or chronic infection, are contra-indications to treatment with MTX.

Continued regular monitoring of liver function and full blood count is vital. There is uncertainty around the value of surveillance liver biopsy in patients exposed to MTX for prolonged periods of time. In some centres, the advent of the Fibroscan (Transient Elastography) to measure liver fibrosis is increasingly obviating the need for biopsy. Its advantages are that it is non-invasive and cheaper, does not carry the risk of pain and bleeding, and avoids the sampling errors inherent in biopsy. Interpretation and subsequent recommendations require close collaboration with gastroenterology.

Co-treatment with folic acid is advised to limit toxicity. A typical protocol is folic acid 5–10 mg once weekly. Pregnancy should be excluded in females before starting treatment, and both men and women receiving MTX must employ effective contraception. British authorities advise continuing contraception for men and women for at least 3 months after stopping MTX. North American advice is that pregnancy should be avoided for at least 3 months after treatment in male patients, and for at least one ovulatory cycle in females. International guidelines on the use of MTX in sarcoidosis provide a resource for developing local management guidance and shared-care monitoring protocols for primary care physicians [8].

Azathioprine

Azathioprine is a purine analogue. Its precise mechanism of action in sarcoidosis is unclear. Its metabolite mercaptopurine affects RNA and DNA synthesis, thereby inhibiting lymphocyte proliferation. Cellular immunity is suppressed to a greater degree than humoral immunity. There are no randomised controlled trials of azathioprine in sarcoidosis. Case series have shown it can improve chest X-ray appearances and reduce breathlessness; however a retrospective review suggested benefit in only two out of ten patients. An open-label study examined the effect of azathioprine (2 mg/kg per day) combined with glucocorticoid treatment in 11 patients with chronic or relapsing pulmonary sarcoidosis [9]. All patients had significant symptomatic relief and showed improved radiographic and physiological parameters, without significant side-effects, despite reducing their prednisolone dose to 0.1 mg/kg/day within 2–3 months of starting the study. Cytokine release in BAL fluid was reduced. Eight patients remained in stable remission for between 4 months and 6 years after stopping treatment.

Regular blood counts to check for myelosuppression, and liver function monitoring, are essential. Azathioprine is metabolised by the enzyme thiopurine methyltransferase (TPMT), and the risk of myelosuppression is increased in the minority of the population who are homozygous for low TPMT activity. Consequently, many clinicians check TPMT levels before starting azathioprine, despite limited evidence to support this practice. Azathioprine should not be started in pregnancy, as there have been reports of premature birth and low birth weight following exposure; spontaneous abortion has been reported after both maternal and paternal exposure.

Hydroxychloroquine

Hydroxychloroquine (like chloroquine) is an anti-malarial agent, which has been used with some success in patients with hypercalcaemia, cutaneous disease, and neurosarcoidosis. Two randomised controlled trials have compared chloroquine and placebo in pulmonary sarcoidosis [10, 11]. In the early British study, 52 patients who had not received steroids but either had pulmonary infiltrates for 6 months and breathlessness, or progressive lung infiltrates for 6 months, or persistent infiltrates for 1 year, were randomised to receive chloroquine or placebo for 16 weeks. Chloroquine treatment conferred no benefit but resulted in a greater number of adverse events. In the subsequent Canadian study, 23 patients received chloroquine at a dose of 750 mg daily for 6 months, gradually tapering every 2 months to 250 mg daily. Eighteen patients were then randomised to a maintenance group or to an observation group. Patients randomised to the maintenance group had a slower decline in lung function and fewer relapses than those in the observation group. Side effects were mainly limited to the high-dose treatment phase. The authors

conclude that chloroquine should be considered in chronic pulmonary sarcoidosis; in practice, hydroxychloroquine is preferred because it has lower ocular toxicity.

Hydroxychloroquine should be used with caution in liver or renal impairment, and regular blood count monitoring (to check for agranulocytosis and thrombocytopenia) and liver function is needed. The British Royal College of Ophthalmologists advises that patients should be asked about visual impairment before starting treatment, and that visual acuity should be recorded. If eye disease is present, an ophthalmologist should be consulted before starting treatment. Patients should be asked about visual symptoms during treatment, and visual acuity monitored annually. If treatment is required for over 5 years, individual arrangements should be made with the local ophthalmology service.

Hydroxychloroquine should be used in caution in glucose-6-phosphate (G6PD) deficiency, as it may precipitate acute haemolytic anaemia. As deficiency is highly prevalent in Africans, in whom persistent and severe sarcoidosis is more common, it appears prudent to check G6PD levels before starting hydroxychloroquine.

Mycophenolate

Like azathioprine, MMF is an anti-proliferative immunosuppressant. However, it is metabolised to mycophenolic acid, which has a more selective action than azathioprine. Several authors report employing MMF successfully as a steroid-sparing agent in extra-pulmonary sarcoidosis, but there are no controlled studies in pulmonary disease. In practice it may be used empirically when other options, including corticosteroids, MTX and azathioprine, have been exhausted.

Leflunomide

Leflunomide is an anti-metabolite similar to MTX, with reduced gastrointestinal toxicity. There are no randomised controlled trials in sarcoidosis, and evidence in favour of its use comes from small case series. Some authors report successful use in sarcoidosis, extrapolating from experience in rheumatoid arthritis.

Minocycline

Minocycline has been used in cutaneous sarcoidosis; one study of 12 patients showed effectiveness in treating skin lesions in 10 patients, and in treating pulmonary involvement in two patients. Possible modes of action of tetracyclines in sarcoidosis include inhibition of matrix metalloproteinases, angiogenesis, apoptosis, and granuloma formation.

Ciclosporin A

Ciclosporin A is a T cell suppressor which has been reported to improve neurosarcoidosis in retrospective studies. However, a randomized controlled trial in 37 patients with pulmonary sarcoidosis treated over 18 months showed no effect on breathlessness or lung function, and side-effects were significantly greater in the treatment group. It is not therefore currently recommended for pulmonary sarcoidosis.

Cyclophosphamide

Cyclophosphamide is an alkylating agent which has been used with apparent benefit in cardiac and neurosarcoidosis. There are no controlled studies in pulmonary disease, and routine use is therefore not currently recommended.

Anti-TNF agents

Agents which more specifically target TNF-α include thalidomide, pentoxifylline, infliximab, and etanercept. Individual case reports and small series support the use of thalidomide in cutaneous sarcoidosis, but there are no studies in pulmonary disease. Teratogenic concerns strictly limit its use in women of child-bearing age, and side-effects can be troublesome. Pentoxifylline in high doses has been shown to improve lung function in mild pulmonary sarcoidosis.

Infliximab is a chimeric humanised monoclonal antibody that neutralises TNF-α. Its effectiveness in sarcoid was first reported in refractory cutaneous and pulmonary disease in 2001. Since then a series of case reports and small series have noted the effectiveness of infliximab in skin, eye, brain, lung, sinus, and muscle disease. Two larger studies were published in 2006. The first, by Doty and colleagues, was a retrospective study of

ten patients with sarcoidosis refractory to conventional agents [12]. Six patients had lung involvement, although the indication for using infliximab was extra-pulmonary disease. Nine patients reported symptomatic improvement with infliximab, and all had objective evidence of improvement. In five of six patients taking concomitant corticosteroids, the dose was reduced. The authors did not comment on lung function or radiology. They nevertheless concluded that infliximab appeared safe and effective in refractory sarcoidosis.

The second study, conducted by Baughman and colleagues [13] was a phase II, multi-centre, double-blind, placebo-controlled clinical trial in which patients were randomised in a 1:1:1 ratio to receive intravenous placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at weeks 0, 2, 6, 12, 18, and 24. Patients were followed up for 1 year. One hundred and thirty eight patients were randomised; 44 completed the placebo arm, 46 completed the lower dose infliximab arm, and 45 completed the higher dose infliximab arm. In all cases the indication for recruitment to the study was refractory pulmonary disease. Patients in the combined infliximab groups had an average increase in forced vital capacity (FVC) of 2.5% predicted at week 24. Post hoc exploratory analyses suggested that patients with more severe disease (longer disease duration, lower FVC or more symptoms) benefit the most.

Although these benefits appear modest, they are significant in patients with life-threatening fibrotic disease who would also potentially be candidates for transplantation. Even stability represents a significant treatment response, and improvement would be exceptional.

Etanercept is a soluble TNF-α receptor fusion protein that binds TNF-α and has a longer half-life than the native soluble receptor. It has not been shown to be effective in sarcoidosis, possibly because it is inferior to infliximab in achieving tissue penetration and cell-mediated lysis of TNF-α secreting cells.

Adalimumab is a fully human anti-TNF-α antibody. A few case reports and small series have reported benefit in extra-pulmonary sarcoidosis. Golimumab is a humanised anti-TNFα antibody, and ustekinumab is a monoclonal antibody which inhibits IL-12 and IL-23. A placebo-controlled trial of these agents in patients with chronic pulmonary and/or skin sarcoidosis failed to demonstrate effectiveness in lung disease, although there was a trend towards improvement in cutaneous disease with ustekinumab.

At present, therefore, infliximab may be considered in life-threatening pulmonary sarcoidosis when all other options have been exhausted. It remains expensive, and patients need careful assessment for evidence of TB before starting therapy.

Important Complications of Treatment

In patients with sarcoidosis requiring treatment, preventing, monitoring for, and managing potential side effects is an important component of clinical follow-up. Several studies have shown that weight gain, skin thinning, sleep disturbance, osteoporosis, and neuropsychiatric disorders occur not infrequently in patients taking corticosteroids, even at relatively low doses. There is limited guidance for clinicians on monitoring for adverse effects in sarcoidosis. Some may arise with little warning; others are potentially preventable by using the lowest steroid dose possible, careful monitoring, and appropriate prophylaxis. They appear to be dependent on dose and duration of treatment. More recent data reinforce previous observations suggesting that oral corticosteroids significantly increase the risk of infection. Diabetes is a notable potential complication, and appropriate monitoring is required.

There is increasing recognition that rapid decline in bone mineral density (BMD) begins in the first 3 months of glucocorticoid use, with a peak after 6 months and further slow decline with continued treatment. This has justifiably heightened concern about the impact on fracture risk. Although Afro-Americans may be at a lower risk of glucocorticoid-induced osteoporosis, a study of BMD in women with sarcoidosis has suggested that post-menopausal women with sarcoidosis may be at greater risk of bone mineral loss compared with controls.

The American College of Rheumatology (ACR) 2010 recommendations for prevention and treatment of glucocorticoid-induced osteoporosis adopt a risk-stratification approach [14]. After measurement of the T score with dual-energy X-ray absorptiometry (DEXA), and taking into account the patient's age, gender, and ethnic origin, the patient's 10-year fracture risk, using the WHO Fracture Risk Assessment Tool (FRAX), is categorised as low, medium, or high. Other risk factors for osteoporosis are low body mass index, parental history of hip fracture, current cigarette smoking, and alcohol intake in excess of three drinks a day. The daily dose and duration of glucocorticoid therapy are taken into consideration. Patients with any of these additional risk factors may be placed in a higher risk category at the clinician's discretion. Bisphosphonates and/or lifestyle measures are advised according to the patient's risk, age, and glucocorticoid exposure, and in women, their child-bearing potential.

British guidelines on prevention and management of glucocorticoid-induced osteoporosis were published in 2002 [15]. Evaluation of all patients taking corticosteroids for three or more months is recommended. General measures advised in all cases include minimising the corticosteroid dose, considering steroid-sparing agents, and switching to topical steroids where possible. Lifestyle measures recommended for all patients include ensuring adequate calcium and vitamin D intake, regular weight-bearing exercise, maintenance of a healthy body weight, smoking cessation, and avoidance of alcohol abuse. In patients with a T score above 0, repeat DEXA is not advised unless very high doses of corticosteroids are required. In patients with a T score between 0 and −1.5, repeat DEXA is advised after one to 3 years if steroids are continued. If the T score is −1.5 or lower, specific treatment is advised in addition to lifestyle measures. Specific treatments include alendronate, cyclical etidronate, hormone replacement therapy in women, pamidronate, and risedronate.

The National Institute for Health and Care Excellence (NICE) recommends DEXA scanning in patients taking prednisolone at doses of 7.5 mg or more daily for 3 months or more [16]. BTS guidelines advise using bisphosphonates as appropriate to minimize steroid-induced osteoporosis. Hypercalcaemia and hypercalcuria arising in sarcoidosis may be exacerbated by supplementary calcium and vitamin D. Some authors therefore advise measuring baseline serum and urine calcium and repeating measurements 4–8 weeks after starting calcium supplements, with continued subsequent monitoring.

A further consideration in sarcoidosis is that patients are relatively young, with females often of reproductive age. Since manufacturers caution against bisphosphonates in pregnancy, physicians must either not prescribe these agents in females of child-bearing age or else counsel them appropriately. Local guidelines should be followed when deciding whether to refer to an osteoporosis clinic.

Since the first report in 2003, hundreds of cases of bisphosphonate-associated mandibular osteonecrosis have been described. This complication has mostly been associated with intravenous pamridonate and zoledronic acid. It may arise spontaneously or follow an invasive procedure such as dental extraction. Length of treatment is a risk factor, especially if it exceeds 36 months. An initial dental examination with appropriate preventative dentistry should be considered before starting a bisphosphonate. Patients with risk factors should be advised to avoid invasive dental procedures while on treatment, if possible.

Opportunistic infections are a potential consequence of immunosuppression. Prophylaxis against pneumonia caused by *Pneumocystis jiroveci* should be given to all patients with a history of the infection, and should be considered for severely immunocompromised patients. North American guidelines for preventing opportunistic infection in HIV-infected individuals, endorsed by the British Infection Society, provide the basis for current recommendations. Oral co-trimoxazole is the drug of choice for prophylaxis, either 960 mg daily or three times a week. The dose can be reduced to 480 mg daily to improve tolerance. In patients unable to tolerate co-trimoxazole, nebulised pentamidine is effec-

tive, as is oral dapsone; atovaquone has also been employed. Co-trimoxazole and dapsone can cause bone marrow suppression and skin rashes, among other side-effects. Neither North American nor British sarcoidosis guidelines recommend Pneumocystis prophylaxis routinely in otherwise immuno-competent patients.

Lung Transplantation

A small number of patients with severe and progressive pulmonary sarcoidosis, despite medical therapy, may be candidates for transplantation. Patients should be assessed for common co-morbidities as well as bronchiectasis, right ventricular impairment, infection, and mycetomas. Close liaison with the transplant centre is required at an early stage.

Sarcoidosis patients represent up to 2% of lung transplant recipients worldwide; median survival is around 5 years. Sarcoidosis is the most common disease to recur in transplanted lung, with reported recurrence rates of 35–60%, but it appears to have a good prognosis, often being asymptomatic and self-limiting.

Conclusions

Having made a diagnosis of sarcoidosis, it is important to remember that around two-thirds of patients achieve spontaneous remission. Many patients will not, therefore, need treatment. Although it is difficult to predict which patients will develop long-term sequelae, those with acute onset of symptoms and stage 0 or I disease generally have the best prognosis. Those with multi-system involvement require joint management with the relevant specialists.

Treatment is not indicated for asymptomatic stage 0 or I pulmonary disease, or for patients with asymptomatic stage II or III disease with mildly impaired, stable lung function. Oral corticosteroids may be indicated for patients with progressive stage II, III, or IV disease. Absolute indications for systemic corticosteroid treatment include hypercalcaemia, neurological, cardiac, or ocular involvement.

Serum ACE levels are more useful for follow-up—especially when monitoring response to treatment—than they are in diagnosis. There is still limited evidence to guide clinicians on the optimum timing for starting treatment and for how to long to treat. Patients with repeated relapses may need long-term steroids with or without additional immunosuppression. Inhaled steroids may be of value for treating intractable cough.

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