Sarcoidosis

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Around 3000 new cases of sarcoidosis are diagnosed each year in the United Kingdom.[1] General practitioners play a key role in the early recognition of the most common clinical presentations of this multifaceted disease, and they usually direct initial assessment and specialist referral. Although prognosis is excellent for most patients, a minority will develop life threatening complications and may need potentially toxic treatments. Most patients are young and understandably alarmed at having sarcoidosis, which can be difficult to explain and understand. This review provides a summary of the management of sarcoidosis and includes updates from the recently revised British Thoracic Society (BTS) guidelines.[2]

What is sarcoidosis and who gets it?

Sarcoidosis is a multisystem granulomatous disease of unknown cause, first described in 1877.[3] Although sarcoidosis may occur at any age, it is usually seen in adults under the age of 50. It is slightly more common in women and certain racial groups, such as African-Americans and Scandinavians. Estimates of incidence and prevalence vary widely. In a well conducted five year study from a health maintenance organisation in the United States, annual age adjusted incidence was 10.9 per 100 000 for white Americans and 35.5 per 100 000 for African-Americans. The lifetime risk of sarcoidosis was estimated at 0.85% for white Americans and 2.4% for African-Americans.[4] In a UK general practice with 10 000 patients, one to two patients will develop sarcoidosis each year.

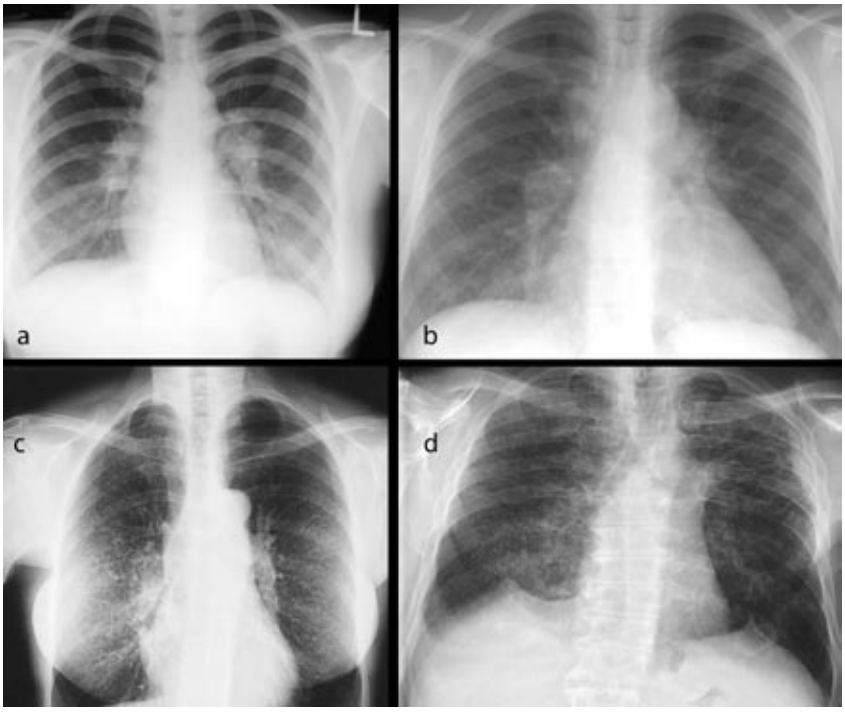

Fig 1 | Patients with sarcoidosis may present at any radiographic stage. Panel (a): stage 1—bilateral hilar lymphadenopathy only (likelihood of spontaneous remission 55-90%); panel (b): stage 2—bilateral hilar lymphadenopathy plus pulmonary infiltrates (40-70%); panel (c): stage 3—pulmonary infiltrates only (10-20%); panel (d): stage 4—pulmonary fibrosis (0%)

How does it present?

Sarcoidosis is remarkable in that it can affect any organ. Some common patterns of presentation are discussed below, with an estimate of how frequently they are seen; these estimates are based on data from US and European studies.[5,6] Up to half of patients have asymptomatic disease, which is sometimes identified when chest radiography is performed for other reasons.[w1]

Lungs (>90%)—Non-productive cough, breathlessness, and sometimes wheeze (if endobronchial involvement is present) are common. Chest examination may be normal, despite an abnormal chest radiograph (fig 1). In more advanced disease fine interstitial crackles may be audible, particularly anteriorly, because the disease has a predilection for the upper lobes. Finger clubbing is rare, and when present alternative diagnoses should be considered—for example, malignancy; other forms of chronic lung disease, such as bronchiectasis or idiopathic pulmonary fibrosis; or infection, such as tuberculosis.

SUMMARY POINTS

- Sarcoidosis is a multisystem granulomatous disease of unknown cause, typically affecting young and middle aged adults
- Three thousand new cases are diagnosed each year in the United Kingdom
- Any organ can be affected—mostly lungs, skin, and eyes—and patients often feel tired and generally unwell
- Most patients do not need systemic treatment, and disease often regresses spontaneously, especially in those presenting with erythema nodosum
- A minority have potentially life threatening progressive organ dysfunction; these patients need active management including oral corticosteroids

The pleura can be affected, but this is unusual. Patients who develop pulmonary fibrosis can develop secondary complications including infection (aspergilloma, mycobacterial), pneumothorax, respiratory failure, and cor pulmonale (fig 1).

Fatigue (66%)—Profound fatigue is under-recognised by health professionals. It is present in two thirds of patients and has a negative effect on quality of life.[6 7] It may be associated with fever, weight loss, general malaise, depression, and raised C reactive protein.

Skin (24%)—Erythema nodosum is one of the most recognisable manifestations of sarcoidosis (fig 2). Lofgren's syndrome (erythema nodosum, arthralgia, systemic malaise, and bilateral hilar lymphadenopathy on chest radiography) is associated with an excellent prognosis, and patients usually recover spontaneously.[w2 w3] A wide variety of other skin abnormalities may be seen, including maculopapular lesions, lupus pernio (often associated with more chronic disease), nodules, and hyperpigmentation or hypopigmentation. Ask the patient about scars, such as appendicectomy scars or tattoos, because these are often infiltrated by granulomas and are easy to biopsy (fig 3).[w4]

Lymphadenopathy (15%)—Extrathoracic lymphadenopathy is common and may cause alarm, given the possibility of diagnoses such as lymphoma and tuberculosis. Fine needle aspiration, or ideally excision biopsy, can lead to rapid diagnosis.

Ocular (12%)—Sight threatening uveitis is a complication of sarcoidosis, and patients may not always be symptomatic—for example, if they have posterior uveitis—so a slit lamp examination of the eyes is mandatory in all patients. Uveoparotid fever (Heerfordt's syndrome) includes a combination of uveitis, parotid gland enlargement, and facial nerve palsy.[w5] Many other ocular problems can occur including conjunctival nodules, lacrimal gland enlargement, cataracts, glaucoma, retinal ischaemia, optic neuropathy, and papillo-oedema.[w6]

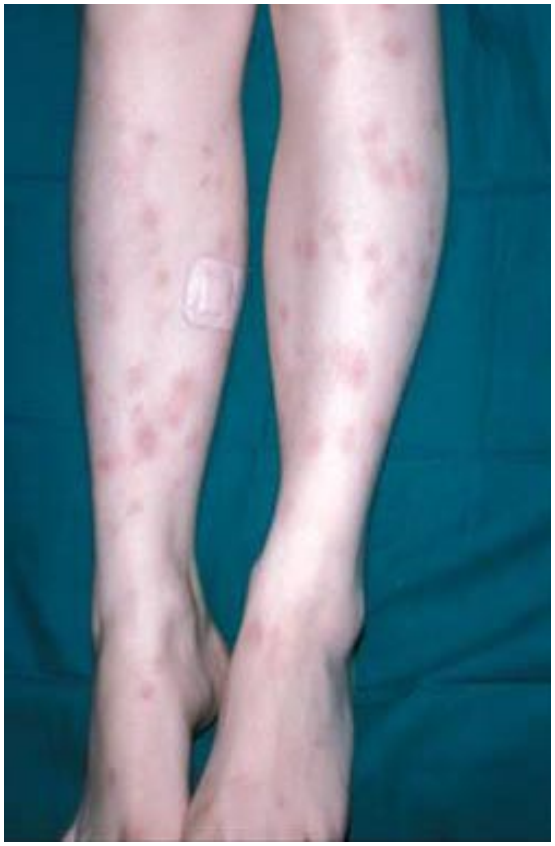

Fig 2 | Erythema nodosum in a patient with sarcoidosis

Hepatic or gastrointestinal (18%)—Typically this is asymptomatic, with liver enzymes being slightly raised. Hepatosplenomegaly, intrahepatic cholestasis, and portal hypertension are rare.[w7]

Renal (5%)—Extrarenal production of calcitriol by macrophages can result in renal calculi, nephrocalcinosis, interstitial nephritis, and renal failure.[w8]

Neurological (5%)—This is a rare yet potentially devastating complication of sarcoidosis, especially if the central nervous system is affected. It includes meningeal inflammation or infiltration, hypothalamic-pituitary effects (for example, diabetes insipidus), encephalopathy, vasculopathy, seizures, aseptic meningitis, hydrocephalus, and mass lesions. Effects on the peripheral nervous system include cranial nerve palsy, most commonly facial, and peripheral or small fibre neuropathy.[w9]

Cardiac (2%)—Although rare, this can cause sudden death so all patients with cardiac symptoms, such as palpitations or abnormalities on electrocardiography, should be referred for specialist cardiology assessment, typically including a Holter monitor, echocardiography, and cardiac magnetic resonance imaging or positron emission tomography. Electrophysiological studies may also be helpful.[w10]

Bone, joint, or muscle (0.9%)—Arthralgia is the most common locomotor symptom. Rarely, bone cysts can occur and muscles can be affected (nodules, myositis, or chronic myopathy).[w11]

Mode of presentation and severity of disease are influenced by ethnicity and sex. African-Americans are more likely than Europeans to develop skin, liver, lymph node, and ocular disease, often with greater severity. Erythema nodosum, commonly seen in white Europeans, is rare in black and Japanese people. In a large US study of patients with recently diagnosed sarcoidosis, women were more likely to have eye and neurological involvement, erythema nodosum, and to be aged 40 years or more, whereas men were more likely to have hypercalcaemia.[5]

How should suspected sarcoidosis be investigated before hospital referral?

History—A detailed history is needed, remembering that sarcoidosis may have extrapulmonary symptoms often relating to skin, eyes, and joints. Consider the possibility of alternative diagnoses that can mimic sarcoidosis. For example, tuberculosis and lymphoma can also cause bilateral hilar lymphadenopathy on chest radiography. A detailed history of occupational and environmental dust exposure may suggest diagnoses such as hypersensitivity pneumonitis. Some patients will have a family history of sarcoidosis.[8]

Examination—Symptoms will help direct clinical examination and may identify potential biopsy sites,

such as lymphadenopathy, skin lesions, old scars, and tattoos (fig 3).

Blood tests—A full blood count, liver function tests, and measurement of serum electrolytes, calcium, and immunoglobulins should be performed. Immunoglobulin measurements can help exclude common variable immunodeficiency, which can present in a similar way but is associated with reduced IgG and IgA (and sometimes IgM) rather than the polyclonal gammopathy usually seen in sarcoidosis.[w12] Many clinicians check serum angiotensin converting enzyme (ACE) concentrations, although BTS guidelines suggest it has a limited role in diagnosis and does not contribute to monitoring patients when added to serial lung function and imaging. Furthermore it has limited sensitivity and specificity,[w13] and because values are influenced by *ACE* gene polymorphisms.[w14]

Chest radiography—Chest radiography allows the disease to be staged, which is of prognostic value (fig 1). Comparison with previous chest radiographs (or reports) can be helpful.

Urine dipstick—This is a standard test in any patient with suspected interstitial lung disease, principally to exclude vasculitis and nephritis.

Spirometry—Spirometry is mandatory in patients with respiratory symptoms.

Electrocardiography—Look for evidence of arrhythmia or conduction delay, which can identify latent cardiac sarcoidosis.[w10]

What tests are used in hospital?

Tissue diagnosis

This will be necessary in most patients, but a clinical diagnosis may suffice (fig 2) in those with a classic presentation, such as Lofgren's syndrome. Common biopsy sites include skin, peripheral nodes, lacrimal glands, and conjunctiva. If the lungs are affected, bronchoscopy with biopsy of central (endobronchial) and peripheral (transbronchial) airways is helpful. Patients with mediastinal lymphadenopathy may need a mediastinoscopy.

Importantly, non-caseating granulomas (fig 4) are a non-specific finding and not diagnostic of sarcoidosis.[9] Granulomatous conditions that can mimic sarcoidosis include lymphoma, mycobacterial infections (notably tuberculosis), and fungal infections. Less commonly, sarcoid-like granulomas can form in response to malignancy, foreign bodies, occupational exposure to beryllium, and in common variable immunodeficiency.[w12] Some medical treatments—for example, interferon alfa for hepatitis[w15] or highly active antiretroviral therapy for HIV infection,[w16] can promote granulomatous reactions. Pathologists routinely stain tissue samples to exclude mycobacterial and fungal disease, although false negative stains do occur, and ideally tissue should also be sent (in saline rather than formalin) to microbiology for prolonged culture.

Tuberculin skin test (Mantoux)

This test is classically negative in patients with sarcoidosis because activated T cells are sequestered in the lung, leading to peripheral depletion. If the test is positive, this raises the possibility of tuberculosis, which must be actively excluded.

Further imaging

A high resolution computed tomography scan of the chest is a standard investigation; it assesses pulmonary involvement, strengthens diagnostic confidence, and identifies abnormal nodes for biopsy. In more advanced disease it can detect complications such as fibrobullous disease, aspergilloma, and bronchiectasis. Gadolinium enhanced magnetic resonance imaging should be considered in patients with suspected myocardial sarcoidosis or neurosarcoidosis. Radionuclide imaging techniques can provide functional imaging of pulmonary and extrapulmonary lesions.[w17 w18] Gallium-67 uptake correlates well with alveolar inflammation because the agent localises to alveolar macrophages, but this technique has limited spatial resolution. Integrated fluorodeoxyglucose-positron emission tomography-computed tomography imaging has better diagnostic performance and can identify areas of sarcoidosis not detected by ^{67}Ga imaging (fig 5). It is also useful for monitoring response to treatment in patients with multisystem and complex forms of disease.[w17 w18]

Detailed pulmonary function tests

The severity of lung disease, disease progression, and response to treatment are assessed by spirometry, gas transfer, and an exercise test. They may be normal in milder disease, but spirometry typically becomes restrictive in pulmonary fibrosis (although it can be obstructive if there is endobronchial involvement). As the disease progresses, gas transfer may be impaired and exercise associated desaturation may occur.

Ophthalmology review

Guidelines recommend that all patients should have a slit lamp examination to identify symptomatic

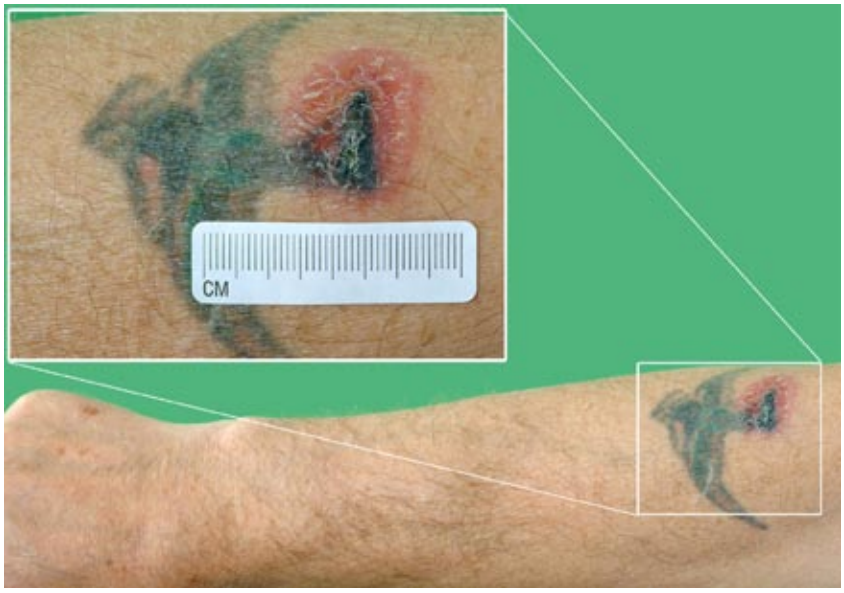

Fig 3 | Forearm of a patient with cutaneous sarcoidosis affecting the tail of his swallow tattoo, confirmed on biopsy. The inflammation resolved with treatment

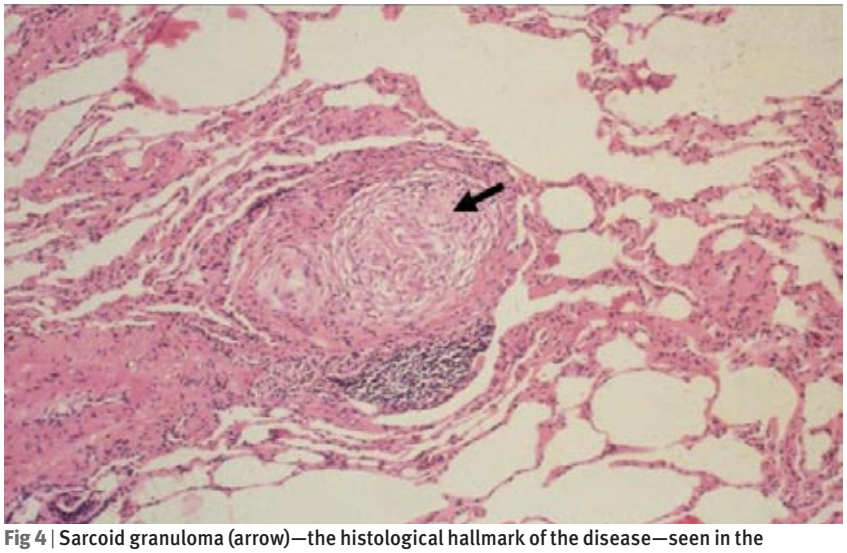

Fig 4 | Sarcoid granuloma (arrow)—the histological hallmark of the disease—seen in the interstitium of the lungs, but found potentially in any organ (magnification ×100, haematoxylin and eosin stain)

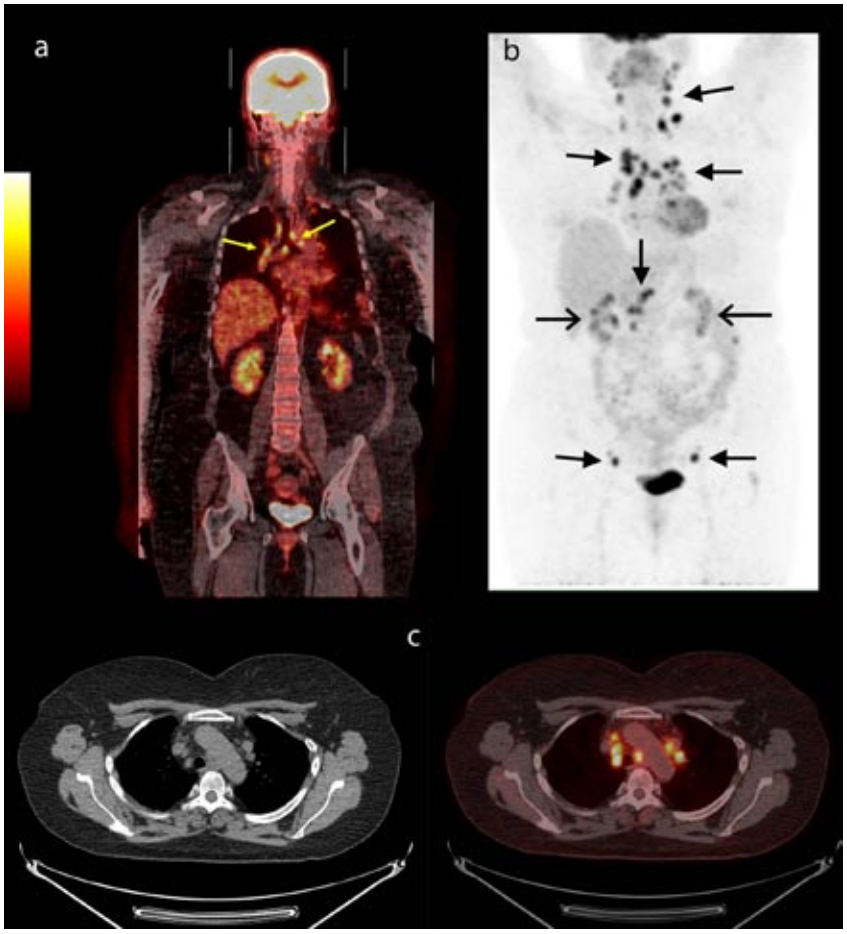

Fig 5 | Integrated fluorodeoxyglucose positron emission tomography-computerised tomography can identify biopsy sites and extrapulmonary disease. In this patient with sarcoidosis, the technique identified active disease, the extent of which was not apparent on computed tomography imaging alone. Panel (a) is a fusion image showing increased uptake in mediastinal nodes (arrows); panel (b) is a maximum intensity projection image showing increased uptake in neck, mediastinal, coeliac, and inguinal nodes (closed arrows) and physiological uptake in kidneys (open arrows); panel (c) is an axial computed tomography and fused image at the level of the aortic arch showing increased fluorodeoxyglucose uptake in prevascular, left paratracheal, and right paratracheal nodes, none of which are enlarged by conventional size criteria

and potentially sight threatening uveitis that needs treatment.[9 w6]

What causes sarcoidosis?

The cause of sarcoidosis remains elusive.[10] The current hypothesis is that it occurs in genetically susceptible people exposed to specific but unknown environmental agents.[11] Evidence for genetic susceptibility comes from multiple family and case-control studies, recently comprehensively reviewed.[12] A major association has been suggested between sarcoidosis and the class II major histocompatibility complex region (MHC) of chromosome 6. Particular phenotypes of sarcoidosis such as Lofgren's syndrome seem to be associated with particular MHC haplotypes—for example, erythema nodosum or Lofgren's syndrome is strongly associated with *HLA* DQB1*0201 in British and Dutch patients.[w19] A mutation of another MHC gene, *BTNL-2*, is associated with sarcoidosis and other inflammatory disorders; the product of the non-mutated gene inhibits the proliferation of T cells.[w20]

Epidemiological studies have reported clustering of cases within families, geographically and seasonally.[w21] Geographical clusters suggest person to person transmission or shared exposure to an environmental agent. Case clustering in winter and early spring is reported. Suggested infective triggers, such as mycobacteria and *Propionibacterium acnes*, are unconfirmed.[13] Studies exploring occupational risk factors have also been inconclusive, despite detailed occupational and environmental questionnaires, although exposures associated with increased risk include insecticides, agricultural employment, and microbial bioaerosols.[14] A negative association with smoking has often been seen.[w22]

Does it run in families?

Familial clustering of sarcoidosis is well described.[15] In a large multicentre US based case-control study, first degree and second degree relatives of patients with sarcoidosis had a significantly increased risk of sarcoidosis compared with relatives of matched controls. Siblings had the highest relative risk (odds ratio 5.8, confidence interval 2.1 to 15.9).[15] In the UK, a questionnaire based study of 268 patients with sarcoidosis reported that 5.9% had at least one other relative (first, second, or third degree) with biopsy confirmed disease.[8] A recently published Danish-Finnish study found that, compared with the general population, cotwins of affected monozygotic brothers or sisters had an 80-fold increased risk of developing sarcoidosis. The increased risk in dizygotic twins was only sevenfold, suggesting that genetic factors play an important role in susceptibility to the disease.[16]

Immunology of sarcoidosis

This is a complex topic, comprehensively reviewed elsewhere.[w23] Interaction between an unknown antigen and antigen presenting cells is thought to result in a T helper 1 biased CD4 positive response. Affected organs are infiltrated by CD4 positive T cells, and in the lungs a striking T cell alveolitis is seen. A complex

TIPS FOR NON-SPECIALISTS

- Always consider alternative diagnoses, such as lymphoma or tuberculosis. Confirmation with tissue biopsy is needed unless clinical confidence is high
- Remember that granulomatous inflammation is consistent with, but not specific for, sarcoidosis and can occur with other illnesses
- A diagnosis of sarcoidosis is often frightening for patients, and vetted patient information leaflets and website links can be helpful
- Ask about cardiac symptoms, such as palpitations and syncope. Although cardiac sarcoidosis is rare, it can cause sudden death, and early identification may allow lifesaving treatment

inflammatory cascade ensues with other inflammatory cells, notably alveolar macrophages, playing a part. Various chemokines and cytokines are released, ultimately resulting in formation of non-specific inflammatory granulomas (fig 4). In most patients this process regresses spontaneously, but in some patients fibroblasts are recruited and production of matrix proteins increases, ultimately resulting in irreversible fibrosis.

Some investigators have highlighted the "immune paradox" of sarcoidosis—affected organs such as the lungs show an intense immune response, yet relative anergy exists elsewhere (such as the negative response to the Mantoux test).[17] A disequilibrium between effector and regulatory T cells has been hypothesised. For example, patients with sarcoidosis have recently been shown to have reduced numbers of regulatory T cells called CD1d restricted natural killer T cells.[w24] These cells may function as an immunological "brake" and have been shown to protect against disorders with increased CD4 positive T helper 1 responses in animals. Loss of immunoregulation by these natural killer cells could explain the amplified and persistent T cell activity that characterises sarcoidosis and other autoimmune diseases, such as diabetes mellitus and multiple sclerosis.[w24] Patients with Lofgren's syndrome have normal numbers of natural killer cells, which may explain why their prognosis is so good. The role of these and other regulatory T cells in sarcoidosis has been reviewed.[w25]

What is the prognosis?

Sarcoidosis generally has a good prognosis.[18 w26] Many patients are asymptomatic, and spontaneous resolution occurs in as many as 60% of these patients. Nonetheless, some patients do have chronic progressive disease, and mortality has been reported to be 1-6%. The disease can wax and wane, either spontaneously or in response to treatment. Patients with lupus pernio, chronic uveitis, chronic hypercalcaemia, nephrocalcinosis, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neurosarcoidosis, and myocardial involvement have a less favourable prognosis, as do black people and those aged 40 or more at onset.[18 w2]

Who needs treatment?

US guidelines and recently updated BTS guidelines (in collaboration with colleagues from Australia, New Zealand, and Ireland) are excellent and discuss treatment options in detail.[2 9] Treatment decisions should balance the risks of using corticosteroids, the most common treatment, against the potential benefits. A general rule is to consider starting treatment when organ function is threatened. The main conclusions reached are[2]:

- Many patients do not need treatment and the disease may spontaneously regress.
- Erythema nodosum can be painful, and short term use of regular paracetamol and a non-steroidal anti-inflammatory drug can be helpful.
- Treatment is not indicated for asymptomatic stage 1 disease or patients with asymptomatic stable stage 2 or 3 disease who have only mildly abnormal lung function.
- Oral steroids may be of benefit for patients with stage 2 or 3 disease who have moderate to severe or progressive symptoms or changes on chest radiography.
- Absolute indications for oral steroids include hypercalcaemia, neurological involvement, cardiac involvement, or ocular involvement (the last one if topical treatment has failed).
- Inhaled corticosteroids are not beneficial as initial treatment or maintenance treatment, although they are sometimes tried in patients with intractable cough.

What should I do if a patient needs oral corticosteroids?

UK guidelines advocate initial treatment with prednisolone, 0.5 mg/kg/day for four weeks.[2] The dose is then gradually reduced over the next six months, ideally to a maintenance dose of around 10 mg or less a day. To prevent corticosteroid induced bone loss, patients are usually started (empirically) on an oral bisphosphonate, and baseline bone densitometry is performed. Duration of treatment varies but is often six to 24 months at least.

What happens if steroids cannot be reduced or stopped?

Some patients will need more than 10 mg/day of prednisolone to control their sarcoidosis. In these circumstances a "steroid sparing" agent can be added, with the aim of subsequently reducing the prednisolone dose to 10 mg/day or less. Unfortunately, no high quality evidence is available to support the use of treatments commonly cited including hydroxychloroquine, methotrexate, azathioprine, and cyclophosphamide.[19] These drugs can be highly toxic and should be given under expert supervision only. For patients who have failed a trial of these agents, treatment with a tumour necrosis factor inhibitor can be considered. The most commonly used is infliximab, although other agents include etanercept and adalimumab. The use of these inhibitors has recently been expertly reviewed.[20] Factors associated with a good response to these agents

SOURCES AND SELECTION CRITERIA

We searched for papers published between 1966 and March 2009 using appropriate index terms and the National Library of Medicine's computerised search service (providing access to Medline, PreMedline, and other related databases). We also consulted Cochrane database systematic reviews and used our personal archive of references.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

British Thoracic Society (www.brit-thoracic.org.uk)—Recently published guidelines on the initial assessment, investigations, and management of sarcoidosis and other forms of interstitial lung disease are available here

American Thoracic Society (www.thoracic.org/sections/publications/statements/index.html)—Although published nine years ago, these guidelines cover all aspects of the disease

Ongoing clinical trials (www.clinicaltrials.gov)—Involvement in clinical trials will improve our understanding and management of sarcoidosis and other lung diseases. This website provides a useful up to date summary of ongoing trials

Resources for patients

British Lung Foundation (www.lunguk.org/sarcoidosis.asp)—Useful site with links to patient support groups (breathe easy groups)

Sarcoidosis and Interstitial Lung Association (www.sila.org.uk)—UK support group

National Heart Lung and Blood Institute (www.nhlbi.nih.gov/health/dci/Diseases/sarc/sarc_all.html)—Provides comprehensive information for patients

Sarcoid Networking Association (www.sarcoidosisnetwork.org)—US based site with multiple links to resources for patients with sarcoidosis

include more severe pulmonary disease, chronic extrapulmonary disease, longer disease duration, and impaired quality of life.

How effective are corticosteroids in sarcoidosis?

We do not know which dose or duration of corticosteroids is most effective, or whether treatment alters the course of the disease. For patients in whom crucial organs are affected, corticosteroids can be life saving. For patients with milder pulmonary disease the evidence is weak. A systematic review of eight randomised placebo controlled trials of oral or inhaled corticosteroids in patients with pulmonary disease concluded that oral steroids improved appearances on chest radiography and a global score of such appearances, symptoms, and spirometry over three to 24 months. However, it found little evidence of improvement in lung function, and only limited data to indicate that oral steroids affect long term disease progression.[21]

Who should manage these patients?

Patients with sarcoidosis should be offered regular hospital clinic review by the appropriate specialist(s). The lungs are affected in most patients, so chest physicians are usually involved, and BTS guidelines recommend multidisciplinary care at interstitial lung disease clinics.[2] Clinic review is typically every three to six months initially, and more often if drugs have been started. Patients with clinically stable disease are seen less often. Patients with stage 2-4 disease are often followed up indefinitely, but stable patients with milder (stage 0-1 disease) can often be discharged by two years. At hospital visits patients should be assessed clinically (symptoms, signs), radiologically (usually chest radiography), and physiologically (pulmonary function tests). They may need blood tests, especially if they previously had hypercalcaemia, impaired renal or hepatic function, or raised serum angiotensin converting enzyme concentrations. Rarely, patients with progressive pulmonary sarcoidosis, who are otherwise medically fit, are considered for lung transplantation.

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