Acute sarcoidosis: Löfgren's syndrome

Sarcoidosis is a chronic multisystem granulomatous inflammatory disorder. It can present acutely which is known as Löfgren's syndrome. The diagnosis may be missed if clinicians are not aware of its classic presenting features and the appropriate diagnostic investigations.

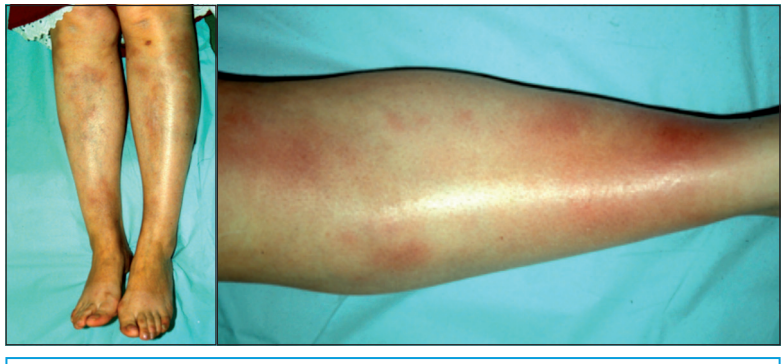
Sarcoidosis is an enigmatic disease that was first observed at the end of the 19th century by three independent pioneers: Jonathan Hutchinson who labeled the disease 'Mortimer's malady', Ernest Besnier who chose the term 'lupus pernio' and Caeser Boeck who first used the term 'sarcoid'. Sarcoid comes from the Greek words sarko and oid, which translated means flesh-like and refers to the skin nodules Boeck observed in affected patients. This similarity to a sarcoma caused Boeck to call the condition 'multiple benign sarcoid of the skin' (Danbolt, 1958). GPs 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. Approximately 3000 new cases are diagnosed each year in the UK and just about any organ can be affected. Although the prognosis is excellent for most patients, a small minority will have potentially life-threatening organ dysfunction often requiring active management (Gribbin et al, 2006). This article reviews acute sarcoidosis in terms of presentation, investigation and treatment as well as the epidemiology and emerging genetic links. In this article the acute form of sarcoidosis will be referred to as Löfgren's syndrome.

Table 1. Causes of erythema nodosum

Bacterial infections	Streptococcus, tuberculosis, chlamydia, yersinia, mycoplasma
Viral infections	Human immunodeficiency virus (HIV), Epstein–Barr virus, herpes simplex virus, hepatitis B and C
Drugs	Antibiotics and oral contraceptives
Malignant disease	Lymphoma
Miscellaneous	Sarcoidosis, ulcerative colitis, pregnancy

Adapted from Requena and Requena (2002)

Figure 1. Erythema nodosum showing the classic bilateral distribution on the shins.



Dr Othman Kirresh *is Rheumatology Registrar in the Rheumatology Department, Medway NHS Foundation Trust, Medway Maritime Hospital, Gillingham,* **Dr John Schofield** *is Consultant Histopathologist in the Histopathology Department, Maidstone and Tunbridge Wells NHS Trust, Maidstone, Kent and Visiting Professor in the School of Physical Sciences, University of Kent and* **Dr Gerald George** *is Consultant Rheumatologist in the Rheumatology Department, Medway NHS Foundation Trust, Medway Maritime Hospital, Gillingham ME7 5NY*

Correspondence to: Dr G George (Gerald.george@medway.nhs.uk)

Pathogenesis

Sarcoidosis is a chronic inflammatory disorder affecting numerous organs and characterized by the presence of non-caseating granulomas. These granulomas are formed as a result of an immune reaction to antigens that remain unknown. The process begins with a CD4 T-cell-mediated inflammation where a granuloma forms. These granulomas will either spontaneously resolve or fibrose, resulting in chronic disease including interstitial lung disease, as Keogh et al (1983) described.

Clinical presentation

Löfgren's syndrome was first described by Sven Halvar Löfgren, a Swedish clinician, in 1953. It is characterized by a triad of bilateral hilar lymphadenopathy with erythema nodosum and/or periarticular inflammation of the ankles, often with a fever (Löfgren, 1953).

Erythema nodosum

Erythema nodosum is a type of panniculitis associated with inflammation of the septa in the subcutaneous fat tissue. It is presumed to represent a delayed hypersensitivity reaction to antigens associated with various agents, drugs and other associated disease. The pathogenesis still remains largely unclear (*Table 1*).

Typically erythema nodosum is sudden in onset presenting with a rash on the anterior aspect of the shins (pretibial) but can also affect the ankles and knees (*Figure 1*). It is characterized by subcutaneous nodules that are warm and erythematous, usually bilateral and tender to touch (Requena et al, 2002).

The presence of erythema nodosum is not necessary to diagnose Löfgren's syndrome, although it occurs in approximately two-thirds of patients (Visser et al, 2002).

Grunewald and Eklund (2007) showed that only 58% of those with acute onset sarcoid and bilateral hilar lymphadenopathy presented with erythema nodosum. Women had an increased predisposition to developing Löfgren's syndrome, comprising 67% of those who had erythema nodosum. Those without erythema nodosum had symmetrical ankle inflammation. It is not unusual for this cohort of patients to be incorrectly diagnosed as having cellulitis as Cheng and Maini (2011) illustrated, particularly as many present with a fever and other systemic features, resulting in antibiotic treatment being given inappropriately.

Musculoskeletal

Acute arthritis is often the first manifestation of Löfgren's syndrome. Most commonly this is oligoarticular, i.e. 2–4 joints and primarily affecting the ankle joints. It may spread to the knees, wrists, elbows, proximal interphalangeal joints and metacarpophalangeal joints. Visser et al (2002) reviewed 55 patients with sarcoid arthritis, and found 87% presented with oligoarthritis and 54 out of the 55 had ankle involvement; 95% of these were bilateral. It can also present as a polyarthritis and less commonly as a monoarthritis. The axial skeleton and sacroiliac joints are usually spared and joint destruction is rare. The arthritis lasts from 2 weeks to 4 months. In a Spanish series by Mana et al (1999), 8% had active disease at 2 years and 6% relapsed after remission.

Bilateral hilar lymphadenopathy and radiology

At the time of presentation the majority of patients will have no respiratory symptoms. It is therefore important to consider Löfgren's syndrome as a differential diagnosis, and it would be prudent to organize a chest X-ray as part of the initial work up. Most commonly seen on chest X-ray are distinct, bilateral enlarged lymph nodes in the hilar and right paratracheal region (Reich et al, 1998) (*Figure 2*). The prognosis of patients with sarcoidosis depends on the stage of disease at presentation. X-ray changes in sarcoidosis can be classified into stages (*Table 2*), ranging from stage 0 (normal) to stage 4 (fibrotic lungs).

High resolution computed tomography is best at defining parenchymal involvement (*Figure 3*) as well as nodal enlargement, and thus is especially useful in patients with normal chest X-rays (stage 0) or those with nodal involvement only (stage 1).

Mana et al (1999) looked at 186 patients presenting with Löfgren's syndrome and found that the majority presented with stage 1 abnormalities (81%), followed by stage 2 (16%) with very few presenting with a normal chest radiograph (3%). Stage 1 disease (hilar adenopathy without pulmonary infiltrates) remits in approximately 60–80% of patients. Stage 2 disease, which has infiltrates, remits in 50–60% of cases and stage 3 (lung infiltrates without bilateral hilar lymphadenopathy) has a lower remission rate of 30%. However, a significant proportion of these patients (25–40%) suffered a relapse 1 month or more after stopping corticosteroid therapy (Lynch et al, 2000).

Epidemiology

Sarcoidosis affects all races, ages and sexes. Hillerdal et al (1984) estimated that the accumulated lifetime risk of sarcoidosis is 1.3% for women and nearly 1% for men but this figure is not specific to Löfgren's syndrome. There are relatively few studies on Löfgren's syndrome as

Figure 2. Chest X-ray demonstrating bilateral hilar lymphdenopathy stage 1.

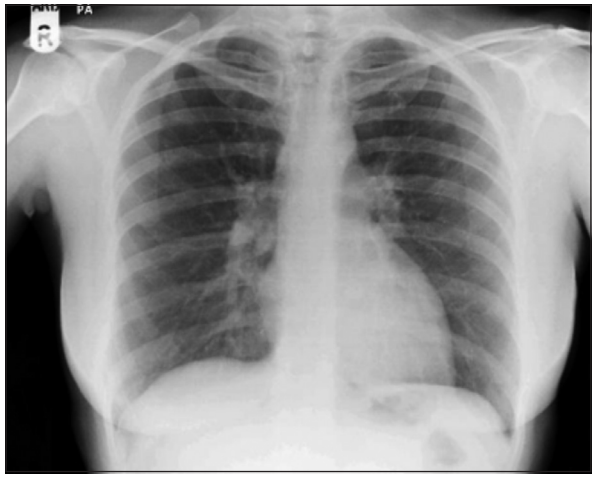
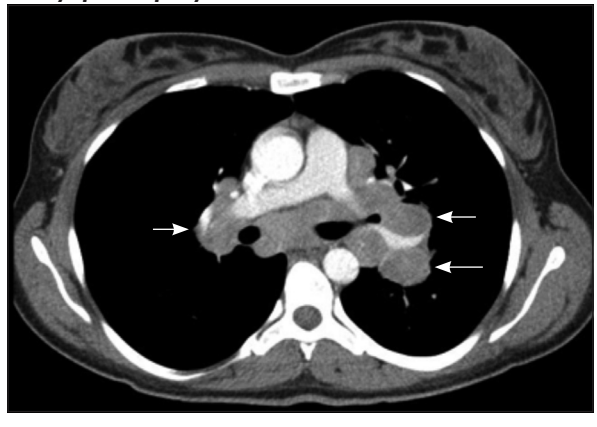


Table 2. Stages of sarcoidosis on chest X-ray

Stage 0	Normal chest X-ray
Stage 1	Bilateral hilar lymphadenopathy
Stage 2	Bilateral hilar lymphadenopathy with abnormal lung parenchyma
Stage 3	Lung parenchymal abnormality without bilateral hilar lymphadenopathy
Stage 4	Significant lung fibrosis

Adapted from Lynch et al (2000)

Figure 3. Chest computed tomography showing stage 1 bilateral hilar lymphadenopathy (white arrows).



a distinct clinical entity. Grunewald and Eklund (2009) performed a large study looking at 301 patients with Löfgren's syndrome, which showed a fairly equal distribution between men and women, 55% and 45% respectively. The peak incidence occurs between 30 and 40 years of age and women have a second peak between 45 and 65 years of age.

The seasonal clustering seen in sarcoidosis is well documented by Bardinas et al (1989), and this phenomenon also exists in patients with Löfgren's syndrome, with the disease onset occurring more commonly in January, April and May. The majority of affected individuals are non-smokers, a trend observed by Peros-Golubicić and Ljubić (1995). Rybicki et al (2001) postulated that familial clustering is also a feature, with first and second degree relatives more at risk of developing the disease. While affecting all races, disease incidence varies between racial and ethnic groups (Luisetti et al, 2000).

Genetics

While the exact cause of sarcoidosis is unknown, it is suspected to arise from interplay between susceptible genes and an environmental trigger. This is supported by the different incidence seen between racial groups and by familial clustering (Rybicki et al, 2001). Löfgren's syndrome is unusual in that it shows a strong genetic link to the HLA-DRB1*03. One of the larger studies of patients by Hillerdal et al (1984) showed 68% were positive for this HLA, as opposed to 17% in a healthy population. Löfgren's syndrome is relatively unusual in some countries such as Japan where the frequency of HLA-DRB1*03 is very low, further supporting the link (Ohta et al, 2006). Another independent genetic risk factor identified is the CCR2 haplotype, and this association is distinct from the HLA genetic link (Spagnolo et al, 2008). Other HLA genetic links have been identified including HLA DQB1*0201. This gene showed a strong association with Löfgren's syndrome in a study by Sato et al (2002) of 803 British and Dutch patients.

Investigations

Baseline tests

Investigation is directed at establishing the diagnosis and assessing the extent and severity of organ involvement. Initial blood tests, including full blood count, may reveal anaemia of chronic disease. An elevated alkaline phosphatase level may be seen in one-third of patients as part of the liver function screen. A bone profile should also be performed as part of the initial work up. Hypercalcaemia as a result of dysregulation of calcium metabolism is a well-recognized complication of sarcoidosis although the prevalence is only 5–10%. When present in acute sarcoidosis further investigation is not necessary, but persistent hypercalcaemia is a poor prognostic factor because of the serious and life-threatening consequences associated with raised calcium levels (Conron et al, 2000). Inflammatory markers including C-reactive protein level and erythrocyte sedimentation rate are likely to be elevated in Löfgren's syndrome and should be checked.

Angiotensin-converting enzyme

Angiotensin-converting enzyme is produced by epithelioid cells of the granulomata and activated alveolar macrophages. Raised serum angiotensin-converting enzyme levels have been linked to sarcoidosis, and are seen in 40–90% of cases. However, elevated angiotensin-converting enzyme levels are seen in other granulomatous diseases and in some non-granulomatous diseases such as Gaucher's, thyrotoxicosis, liver cirrhosis and diabetes mellitus. The British Thoracic Society guidelines report that the role of measurement of angiotensin-converting enzyme levels is limited both in diagnosis and disease monitoring when combined with lung function and imaging as a result of poor sensitivity and specificity (Bradley et al, 2008).

Lactate dehydrogenase

Lactate dehydrogenase may be a useful initial biochemical marker which indicates high cell turnover and lysis (Mana et al, 1999). Similarly lymphoma may present with enlarged hilar lymph nodes. If there is uncertainty about the diagnosis of Löfgren's syndrome it is important to exclude a lymphoproliferative disorder.

Histopathology and biopsy

The diagnosis of sarcoid arthropathy is based upon suggestive clinical, imaging, synovial fluid and, in selected cases, synovial tissue biopsy. The diagnosis of Löfgren's syndrome can be made based upon clinical features alone, therefore a biopsy is not usually required. In a patient with bilateral acute ankle arthritis and hilar adenopathy, with or without the tender red nodules of erythema nodosum, there is a high degree of specificity for the diagnosis of acute sarcoid arthritis (Mana et al, 1999). However, biopsy of the affected organ should be obtained where possible, particularly if there is diagnostic uncertainty, to exclude infection or malignant disease.

The pathognomonic feature of sarcoidosis is a well-formed, rounded non-caseating epithelioid granuloma (*Figure 4*). These can be seen in almost any tissue, but are typically found in lung parenchyma, lymph nodes, liver, spleen and bone marrow. While these granulomata are typical of the disease, they are not specific. Other granulomatous diseases may mimic sarcoidosis and the diagnosis requires exclusion of other causes and an appropriate clinicopathological context. The granulomas are therefore often referred to as 'sarcoid-like'.

The granulomas are composed of aggregates of epithelioid macrophages, small lymphocytes of both B and T cell lineages, and multinucleated histiocytic giant cells. Sometimes laminated or star-shaped calcified structures, schaumann or asteroid bodies are present. There is often some associated fibrosis and collagen

deposition around the granuloma, and there may be a cuff of small T lymphocytes at the periphery.

While impaired T cell function is thought to be an important part of the pathogenesis of the granulomas, patients with depressed helper T cell function may be unable to generate typical granulomas. The T lymphocytes seen in sarcoid granulomata are typically a mixture of CD20-positive small B cell, CD4-positive small T cells and CD8-positive small T cells (Rosen, 2007).

Special tests

Mantoux

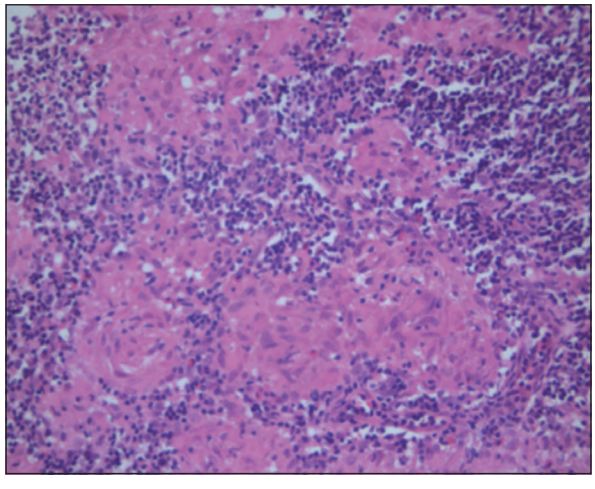
The Mantoux test (also known as the tuberculin skin test) is a screening tool for tuberculosis. It is used to identify individuals with previous sensitization to mycobacterial antigens (latent tuberculosis). It consists of intradermal injection of tuberculin material, which stimulates a delayed-type hypersensitivity response mediated by T lymphocytes and causes induration within 48–72 hours (Comstock, 1999).

It is important to exclude other conditions which may have features that overlap with Löfgren's syndrome. Tuberculosis and atypical myobacterial infections form part of the differential of sarcoidosis and granulomatous lung disease. Tuberculosis may present with both erythema nodosum and bilateral hilar lymphadenopathy. This test is classically negative in patients with acute sarcoid; if positive, further investigations for tuberculosis should be considered (Dempsey et al, 2009).

Pulmonary function tests

Pulmonary function testing may show a restrictive pattern with reduction in vital capacity, residual volume and total lung capacity. Around 65% of patients have airflow limitation at presentation. Bronchoscopy and bronchoalveolar lavage shows a 30–50% lymphocytosis with a CD4:CD8 T-cell ratio >3.5 (Iannuzzi et al, 2007).

Figure 4. High magnification view showing several well-formed non-caseating epithelioid granulomas on a background of small lymphocytes. (Haematoxylin and eosin magnification x200.)



Treatment

Löfgren's syndrome does not usually require treatment as its natural course in the majority of people is to resolve spontaneously. However, the symptoms can be debilitating for patients and symptomatic relief is important. Erythema nodosum can be treated with simple analgesics such as paracetamol. Non-steroidal anti-inflammatory drugs may be used to reduce inflammation and in severe cases a short course of corticosteroids may be necessary. Patients with acute sarcoid arthritis also respond well to non-steroidal anti-inflammatory drugs. Occasionally patients with a severe arthropathy may require a short course of oral corticosteroids (prednisolone 15–40 mg/day) (Iannuzzi et al, 2007).

The British Thoracic Society recommends oral corticosteroids for 6–24 months only in cases of progressive pulmonary disease or extrapulmonary disease requiring treatment. These should be used in conjunction with bisphosphonates for bone protection (Bradley et al, 2008). This is unlikely to apply in the majority of cases of Löfgren's syndrome as 97% have stage 1 or stage 2 chest X-ray changes (Mana et al, 1999).

Prognosis

Löfgren's syndrome has an excellent prognosis. It is estimated that 85% of people with Löfgren's syndrome will make a full recovery within 2 years (MacFarlane, 1984). Interestingly, the presence of HLA-DRB1*03 results in a more favourable prognosis with almost all those with Löfgren's syndrome recovering within 2 years. Those who were HLA-DRB1*03 negative, however, run a 50% chance of having persistent disease (Luisetti et al, 2000).

Conclusions

Löfgren's syndrome is characterized by the triad of hilar adenopathy, acute polyarthritis and erythema nodosum. It is a largely self-limiting illness with spontaneous remission. However, the diagnosis should not be missed in clinical practice and should be included as part of the differential diagnosis in any patient presenting with any of those features. **BJHM**

Conflict of interest: none.

Bardinas F, Morera J, Fité E, Plasencia A (1989) Seasonal clustering of sarcoidosis. *Lancet* **ii**(8660): 455–6

Bradley B, Branley H, Egan J et al (2008) Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* **63**(suppl 5): V1–58

Cheng R, Maini A (2011) Löfgren's syndrome misdiagnosed as cellulitis. *Emerg Med Australas* **23**(3): 376–8

Comstock G (1999) How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* **3**(10): 847–50

Conron M, Young C, Beynon H (2000) Calcium metabolism in sarcoidosis and its clinical implications. *Rheumatology* **39**(7): 707–13

Danbolt N (1958) The historical aspects of sarcoidosis. *Postgrad Med J* **34**(391): 245–7

Dempsey O, Paterson E, Kerr K, Denison A (2009) Sarcoidosis Clinical review. *BMJ* **339**: B3206

Gribbin J, Hubbard R, Jeune L, Smith C, West J, Tata L (2006) Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* **61**(11): 980–5 (doi: 10.1164/rccm.200805-725OC)
Grunewald J, Eklund A (2007) Sex-specific manifestations of Löfgren's syndrome. *Am J Respir Crit Care Med* **175**(1): 40–4
Grunewald J, Eklund A (2009) Löfgren's syndrome: human leukocyte antigen strongly influences the disease course. *Am J Respir Crit Care Med* **179**(4): 307–12
Hillerdal G, Nöu E, Osterman K, Schmekel B (1984) Sarcoidosis: epidemiology and prognosis. A 15-year European study. *Am Rev Respir Dis* **130**(1): 29–32
Iannuzzi M, Rybicki B, Alvin S, Teirstein M (2007) Sarcoidosis. *N Engl J Med* **357**: 2153–65
Keogh A, Hunninghake W, Line R, Crystal G (1983) The alveolitis of pulmonary sarcoidosis. Evaulation of natural history and alveolitis-dependent changes in lung function. *Am Rev Respir Dis* **128**(2): 256
Löfgren S (1953) Primary pulmonary sarcoidosis, early signs and symptoms. *Acta Med Scand* **145**(6): 424–31
Luisetti M, Beretta A, Casali L (2000) Genetic aspects in sarcoidosis. *Eur Respir J* **16**(4): 768–80
Lynch D, Newell D, Jin Seong L (2000) *Imaging of Diffuse Lung Disease.* BC Decker, Hamilton, Ontario, Canada: 79
MacFarlane J (1984) Prognosis in sarcoidosis. *BMJ* **288**: 1557–8
Mana J, Gomez-Vaquero C, Montero A et al (1999) Lofgren's syndrome revisited: a study of 186 patients. *Am J Med* **107**: 240–5
Ohta H, Tazawa R, Nakamura A et al (2006) Acute-onset sarcoidosis with erythema nodosum and polyarthralgia (Löfgren's syndrome) in Japan: a case report and a review of the literature. *Intern Med* **45**(9): 659–62
Peros-Golubicić T, Ljubić S (1995) Cigarette smoking and sarcoidosis. *Acta Med Croatica* **49**(4-5): 187–93
Reich M, Brouns C, O'Connor A, Edwards J (1998) Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest* **113**: 147–53
Requena L, Requena C (2002) Erythema nodosum. *Dermatol Online* **8**(1): 4
Rosen Y (2007) Pathology of sarcoidosis. *Semin Respir Crit Care Med* **28**(1): 36–52
Rybicki A, Iannuzzi C, Frederick M et al (2001) Familial aggregation of sarcoidosis: a case-control etiologic study of sarcoidosis. *Am J Respir Crit Care Med* **164**: 2085–91
Sato H, Grutters JC, Pantelidis P et al (2002) HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. *Am J Respir Cell Mol Biol* **27**(4): 406–12
Spagnolo P, Sato H, Grunewald J et al (2008) A common haplotype of the C–C chemokine receptor 2 gene and HLA-DRB1*0301 are independent genetic risk factors for Löfgren's syndrome. *J Intern Med* **264**: 433–41 (doi: 10.1111/j.1365-2796)
Visser H, Vos K, Zanelli E et al (2002) Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* **61**: 499–504

KEY POINTS

- Löfgren's syndrome is the combination of erythema nodosum, hilar adenopathy, migratory polyarthritis, and fever. The presence of all these features has a high specificity for acute sarcoidosis.
- Erythema nodosum without the other features has a broad differential.
- Approximately 40% of patients with Löfgren's syndrome have elevated angiotensin-converting enzyme levels at presentation; those with elevated angiotensin-converting enzyme levels tend to have a more persistent arthritis.
- Löfgren's syndrome is strongly associated with the presence of HLA-DQB1*0201.
- Löfgren's syndrome has an excellent prognosis and spontaneous remission. Initial treatment with non-steroidal anti-inflammatory agents is usually adequate to control symptoms.