

Topical Reviews

An overview of current research and practice in rheumatic disease



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MUSCULOSKELETAL ASPECTS OF SARCOIDOSIS

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- **Sarcoidosis is important to rheumatologists because it frequently affects the musculoskeletal system, involving joints, muscles and bone**
- **The acute and generally self-limiting form of the disease (Löfgren's syndrome) more commonly affects young white adults and is characterised by diffuse, usually bilateral ankle swelling with or without erythema nodosum and radiological evidence of bilateral hilar adenopathy. It frequently requires no treatment**
- **The more chronic form of the disease affects an older, more commonly black patient population and may involve multiple organ systems. It may prove difficult to diagnose as it may mimic or occasionally coexist with a connective tissue disease with which it may share many clinical features**
- **The chronic form of disease may prove resistant to conventional treatments**

INTRODUCTION

The aetiology of sarcoidosis has eluded scientists and clinicians since the first description of the condition by Hutchinson in London in 1877. Its pathological and clinical features have been well characterised. It is a multisystem granulomatous disorder with typical histomorphometric appearances.

The accumulation of T-lymphocytes, mononuclear phagocytic cells and non-caseating granulomas occurs in involved organs. These granulomas may resolve spontaneously or lead to secondary fibrosis and permanent organ damage.¹⁻³ Sarcoidosis involves the lungs in over 90% of cases and commonly the lymphoreticular system, skin, eyes, muscles and joints. Less commonly other organs, including the heart, kidneys, brain and peripheral nervous system, may be clinically affected (Table 1).

EPIDEMIOLOGY

Sarcoidosis is estimated to affect 10–12 per 100,000 in Caucasian populations but varies widely in both prevalence and incidence with ethnic and geographical differences. Black Americans have been estimated to have a 2.4% lifetime risk of the disease compared to 0.85% in the comparative white population.⁴ Previous studies, predominantly in relation to the incidence of pulmonary disease, demonstrated significantly differing levels among the same ethnic groups living in different geographical locations, suggesting the presence of environmental influences. Sex differences

TABLE 1. Clinical manifestations of sarcoidosis.

Organ/system	Frequency	
	Clinical	Histological
Lung	70%	90%
Reticuloendothelial	40%	
Lymphadenopathy	40%	
Hepatic	20%	75%
Splenic	25%	20%
Skin	20%	
Eye	20%	
Musculoskeletal	25%	
Joints (incl. periarticular)	20%	
Muscle	5%	50%
Bone	4%	
Cardiac	10%	20%
Neurological	5%	
Exocrine	4%	
Kidney		
Hypercalcuria	50%	
Hypercalcaemia	15%	
Nephrocalcinosis	5–10%	
Gastrointestinal	0.5%	
Endocrine/reproductive	<0.5%	

have been reported and in one Swedish study of Löfgren's syndrome women were twice as likely to develop erythema nodosum as men.⁵

AETIOLOGY

The cause(s) of sarcoidosis is/are unknown. It is likely that both environmental and genetic factors are involved.

Evidence for an infective cause

Geographical, occupational and seasonal clustering of sarcoidosis cases suggests involvement of environmental, perhaps infective, factors. Most notably an 'outbreak' of sarcoidosis on the Isle of Man found an increased incidence of the disease in individuals living within 100 metres of one another for periods of 5 years before and 2 years after the onset of disease.^{6,7} Similar cohorts in Sweden and Japan have been reported.⁸

Occupational clustering of cases has been reported in servicemen, healthcare workers and firemen⁹⁻¹³ and seasonal clustering, generally with incidence peaks during spring and early summer, has been reported from Greece, Spain, Japan and Sweden.^{5,14-16}

Suggested bacterial disease triggers include mycobacteria and *Propionibacterium acnes*.^{17,18} The incidence of sarcoidosis in young adults matches the high prevalence of acne at the same age and very high DNA copy numbers of *P. acnes* were found in tissue from patients with sarcoidosis.

Genetic factors

First-degree relatives of patients with sarcoidosis have been shown in one large case-control study to carry

an increased risk for developing sarcoidosis, the risk being greatest in a Caucasian population.¹⁹

The most significant finding is a linkage to the major histocompatibility complex on the short arm of chromosome 6. There appear to be several alleles that confer susceptibility (HLA DR11, 12, 14, 15, 17) while others (HLA DR1 and 4 and possibly DQ 0202) may be protective.²⁰

Clinical heterogeneity of disease manifestations has been postulated to be associated with angiotensin-converting enzyme (ACE) gene polymorphism.²¹

PATHOLOGY AND PATHOGENESIS

As indicated above, the initiating events for this disease are still unknown. The most widely accepted theory is that the disease is initiated by inhalation of one or more environmental agents. Indeed studies of incidence following dust exposure after the collapse of the World Trade Centre in New York led to 86 cases of pulmonary disease per 100,000 population in the first year and 22 cases per year for 4 years thereafter, compared with 15 cases per 100,000 during the previous 15 years.²²

A negative effect of cigarette smoking on the incidence of the disease has been reported in several studies;^{23,24} this may reflect reduction in broncheolar T-cell populations.²⁵

The characteristic non-caseating granulomatous lesions of sarcoidosis initially comprise predominantly CD4⁺ T-lymphocytes producing interleukin-2 (IL-2), with the subsequent development of mature lesions composed of tightly-packed centres with macrophages, epithelioid cells and multinucleate giant cells, surrounded by lymphocytes, monocytes, mast cells and fibroblasts.²⁶

The granulomas may resolve or progress to obliterative fibrosis; factors which appear to maintain granulomas include IL-12 whereas resolution may be mediated via IL-10.²⁷ Alveolar macrophages release tumour necrosis factor (TNF) which may be a marker of chronicity and severity of disease along with IL-8 and IL-12.²⁸

ACE is a membrane-bound glycoprotein, dipeptidyl carboxypeptidase, usually derived from pulmonary vascular endothelium and which catalyses the conversion of angiotensin 1 to angiotensin 2. Sarcoid epithelioid cells activated by CD4⁺ lymphocytes lead to elevated levels. This is thought to be due to proteolytic cleavage of the hydrophobic anchor which binds it to the cell membrane, thus allowing passive leakage to occur. The highest blood levels are found with extensive disease, especially when there is prominent lymphoreticular involvement.

The histopathology of extrapulmonary lesions is similar to that of those found in the lungs, but biopsy may be required to differentiate sarcoidosis from other conditions, e.g. tuberculosis.

CLINICAL MANIFESTATIONS

In over 70% of cases the disease presents between the ages of 10 and 40 years and up to half of all cases come to light following routine chest radiography. 90% of patients will have pulmonary involvement, but this is often asymptomatic. Chest examination is rarely abnormal even when extensive radiological changes coexist, but wheezing may be detected.²⁹

Extrapulmonary disease is common and may be the presenting feature in up to 30% of cases.³⁰ Variations in frequency and organ involvement are dependent upon sex, age at onset and ethnicity. Erythema nodosum is twice as common in women with acute sarcoidosis as in men and in white patients compared with black. In contrast, symptomatic pulmonary involvement, constitutional symptoms and lymphadenopathy are more than twice as common in the acute presentation in black and Asian patients compared with white.

The reported prevalence of musculoskeletal features varies between 4% and 38%.³¹ Patients may have one or more features, including arthritis, peri-arthritis, bone disease, myositis and vasculitis.

ARTHRITIS IN SARCOIDOSIS

25% of patients with sarcoidosis have arthritis either as a presenting complaint or in association with other disease features.³² Patients generally fall into one of two patterns: either the acute form with a self-limiting course or a more chronic form with an insidious onset.

Acute arthritis

The typical presentation is with either bilateral diffuse ankle swelling, with or without erythema nodosum, or an oligoarthritis of a reactive type, the former being the more common (see Löfgren's syndrome below). The pattern of acute arthritis is usually oligoarticular with both large and small joint involvement, more in the lower than the upper limb.

In a prospective study of 189 patients presenting with an acute oligoarthritis, 17 (9%) had sarcoidosis, all of whom had bilateral ankle swelling including 10 with Löfgren's syndrome.²³

Löfgren's syndrome This is an acute and benign form of sarcoidosis first recognised and described by Löfgren and Lundbäck^{33,34} in 1952 in which the coincident features of erythema nodosum and bilateral hilar adenopathy are often accompanied by arthralgia or arthritis, uveitis, fever and pulmonary involvement. Subsequently it was recognised that periarticular ankle inflammation, in the absence of

erythema nodosum, was also a variant of the same condition^{35,36} and more commonly seen in men than women.⁵ Indeed, erythema nodosum has been shown in several studies to be more common in Caucasian women than any other group.

A study of 186 patients over a 20-year period in Spain³⁷ confirmed the previous descriptions, with serum ACE levels elevated in 50% of patients. Of the 133 patients followed up for 5 years, only 8 (6%) had recurrent or persistent disease, of whom only 1 patient developed chronic disease. This study also demonstrated that a normal ACE level at presentation was associated with disease resolution in all cases.

Chronic arthritis

The forms of chronic arthropathy – typically involving the hands, wrists, ankles, feet and knees – seen in sarcoidosis include:

- **Dactylitis** – involving one or more digits in the hands, feet or both and often associated with underlying bone involvement (see bone and vascular disease below).³⁸ The important differential from psoriatic arthropathy needs to be made when seen in isolation.
- **Oligo- or polyarthritis** – often with a symmetrical distribution and associated with signs of inflammation including warmth, effusion and typical symptoms of pain and morning stiffness, but rarely with deformity. Synovial histology may reveal non-specific synovitis with or without non-caseating granulomata.^{39,40}
- **Non-erosive deforming arthropathy** – similar to that seen in post-rheumatic fever (Jaccoud's arthropathy) or to that seen in systemic lupus erythematosus (SLE) involving the hands and wrists.⁴¹
- **Tenosynovitis** – occurs either in association with arthritis or (infrequently) alone and involving the Achilles tendon or the flexor tendons in the hands.⁴²

Investigation

Imaging

- **X-rays** – plain radiographs of the joints are usually normal unless there is coexisting bone disease.
- **Ultrasound** – demonstrates soft tissue and periarticular abnormalities, especially around the ankles.
- **Isotope bone scanning** – may show increased uptake in involved joints and especially in bones but is non-specific. Gallium 67 scanning may show increased uptake in joints but does not correlate with the level of local disease activity.
- **Magnetic resonance imaging (MRI)** – may show evidence of true joint synovitis but clearly defines the periarticular nature of inflammation at the ankle in Löfgren's syndrome.⁴³

Histopathology

Synovial biopsy obtained at either arthroscopy or arthrotomy may confirm the diagnosis if typical granulomas are found but often shows non-specific synovitis (see above). Microbiological and polarised light microscopy examination should also be undertaken on biopsy samples to exclude alternative diagnoses.

Diagnosis

In the acute presentation of Löfgren's syndrome, the presence of bilateral diffuse ankle swelling, with or without erythema nodosum, in association with radiological evidence of bilateral hilar adenopathy is often sufficient to establish the diagnosis. Other non-invasive tests which may be helpful include a negative tuberculin skin test (Mantoux) and a gallium 67 scan, which will show hilar or right paratracheal uptake in almost 100% of cases and which may prove positive when the chest radiograph is normal or equivocal. Tissue biopsy may be required, but in a large study of 186 patients, where histological confirmation was obtained, follow-up of those that were biopsy-negative did not reveal any subsequent diagnosis other than sarcoidosis.³⁷

Other forms of sarcoid arthritis, as described above, may present diagnostic challenges unless characteristic systemic features of sarcoidosis, in particular lung disease, are present.

Histological confirmation may be especially important if classical multisystem features are absent or when other conditions are suspected, most notably either tuberculosis or fungal infection, other granulomatous diseases such as Crohn's disease, lymphoma, Wegener's granulomatosis or even rheumatoid disease.

Serum ACE levels are elevated in 75% of patients with untreated sarcoidosis but are not diagnostic as they may be moderately elevated in other disorders. Their use in monitoring the disease course is unproven.

Treatment

There are no good controlled trials of treatment in the arthritis of sarcoidosis. Advice is based upon small studies and against the background of treatments used predominantly for pulmonary disease.

In the arthritis of Löfgren's syndrome, which is usually self-limiting, symptomatic treatment with the following agents has been employed in a stepwise order:

1. **Non-steroidal anti-inflammatory drugs (e.g. ibuprofen or naproxen)** – these may often be sufficient alone or in combination with other treatment
2. **Colchicine** – in a dose of 0.5 mg 2–4 times daily
3. **Hydroxychloroquine** – 400 mg daily (but not more than 6.5 mg/kg body weight per day)
4. **Prednisolone** – 15–20 mg daily.

In more chronic or severe arthritis, or where there is a lack of response to the above regime, drugs such as methotrexate, up to 25 mg per week,⁴⁴ or azathioprine in a dose up to 2.5 mg/kg body weight per day may be used.

A small number of case reports and limited open-label studies have described use of TNF blockade treatment. There is some evidence of therapeutic effectiveness of the monoclonal antibodies infliximab and adalimumab, both of which have been used in the treatment of other disease features.⁴⁵ Etanercept, which has not been shown to be effective in pulmonary disease, may be effective in arthropathy.⁴⁶

MYOPATHY IN SARCOIDOSIS

Muscle involvement is reported in 50–80% of patients with sarcoidosis. In one study³⁷ gastrocnemius muscle biopsy was performed on 122 patients, with positive results in 65 (53%). However, muscle involvement in all but a small number (5%) is asymptomatic.

Myositis may be focal, affecting such areas as the diaphragm,⁴⁷ extraocular muscles⁴⁸ or individual limb muscles, on occasions with a pseudotumour,⁴⁹ or widespread, with unexplained generalised weakness and myalgia.

The generalised myopathy can present in one of two ways: an insidious onset of proximal myopathy with or without an elevated creatinine phosphokinase (CPK) level and poorly-responsive to steroid therapy, or an acute myositis, often in women, with typical elevation of the CPK.⁵⁰

Investigation

Electromyography may show typical myopathic features. Patterns of generalised myotonia may mimic acid maltase disease.

MRI may demonstrate the pattern of muscle involvement, especially with focal or nodular myositis, allowing identification of the appropriate site for muscle biopsy.⁵¹

Muscle biopsy may reveal changes which may be classified as 'early' or 'late'. In the former focal granulomas with giant cells, typical of those seen elsewhere in the disease, with a predominance of CD4⁺ T-cells, are seen, whereas in the latter well-established granulomas are surrounded by CD8⁺ T-cells which themselves infiltrate rather than compress the muscle fibres.⁵² Endomysial and perivascular inflammation coexists with areas of fibre degeneration and regeneration.⁵³ Granulomas may surround intramuscular nerve fibres causing a neuromyopathy.⁵⁴

Treatment

Treatment is dependent upon severity and anecdotal evidence as there are no published controlled trials.

Along with most other features of the disease, corticosteroids are the mainstay of therapy. This is particularly applicable where the disease manifests itself as a frank myositis with high levels of CPK.

The clinician always needs to be aware of the possibility of a steroid-induced myopathy, especially in situations when the patient has already been treated with corticosteroids for other disease features before the onset of myopathy.

Steroid-sparing drugs such as methotrexate or azathioprine may be effective.

Nodular sarcoid muscle lesions when few in number may be successfully treated with local triamcinalone injections.³

BONE DISEASE IN SARCOIDOSIS

Although relatively infrequent, bone disease affects about 5% of patients with sarcoidosis but is asymptomatic in half those affected. Focal lesions often occur in the phalangeal bones. They may be accompanied by dactylitis, on occasions lead to fracture, and are generally associated with more severe and chronic disease.⁵⁵ Typically the lesions have a cystic or lattice-like radiographic appearance and in addition to dactylitis may be associated with marked dystrophy of the nails somewhat like a gross form of clubbing.^{56,57}

Other forms of bone disease may involve the skull directly or may result from direct invasion of the facial and skull bones by granulomatous inflammation. This form of the disease is often accompanied by lupus pernio.

Sclerotic bone lesions rarely occur; they may demonstrate an increased non-specific uptake on an isotope bone scan⁵⁸ and are found more commonly in middle-aged black patients.⁵⁹ Involvement of the long bones may mimic Paget's disease but the alkaline phosphatase level is not usually raised.

Spinal involvement is rare. Sarcoid bony lesions have occasionally been reported in the lower thoracic or upper lumbar vertebrae⁶⁰ and atlanto-axial involvement has been described even more rarely.⁶¹ The lesions may be lytic or sclerotic and are most easily detected using MRI, the lesions being hypointense on T1-weighted images, hyperintense on T2-weighted and enhancing with gadolinium.⁶² Biopsy has been advocated when a lesion involves both vertebral body and disc to exclude an infective cause⁶³ or when a sclerotic lesion is associated with infiltrative features such as cord or nerve root compression. Spondyloarthropathic features have also been described with paravertebral ossification.⁶⁴

Sacroiliitis has rarely been reported until a recent report of 4 cases among 61 patients with sarcoidosis (6.6%) screened for spinal involvement.⁶⁵

Bone density

Few reported studies of bone density in sarcoidosis exist but those there are show an increased prevalence of osteopenia possibly due to diffuse skeletal granulomatosis, calcitriol and osteoclastic activating factor and/or steroid treatment. One study showed 5 of 36 untreated patients had bone density levels more than 2 standard deviations below normal.⁶⁶

Pseudoclubbing

True clubbing is rare but gross nail and nailbed dystrophy occurs, usually in association with underlying bone disease and dactylitis.^{56,57}

Treatment

No controlled trials have been published but anecdotal evidence suggests, along with many other features of the disease, that corticosteroids may be effective. However, caution must be exercised (see below).

Prevention of bone loss is more controversial as calcium and vitamin D are relatively contraindicated due to the increased risk of hypercalcaemia, but calcitonin and bisphosphonates have been used.^{67,68}

VASCULITIS IN SARCOIDOSIS

Vasculitis is rare but has been described in large, medium and small vessels. Large artery granulomatous inflammation of the vessel wall may resemble Wegener's granulomatosis, a disease with which sarcoidosis shares many clinical features but not anti-neutrophil cytoplasmic antibodies.⁶⁹ Large artery involvement may also resemble giant cell or Takayasu's arteritis. Large vessel disease may be a discrete entity or overlap with Blau syndrome (rash, iritis, granulomatous arthritis and a poor prognosis), an autosomal dominant form of the disease.⁷⁰ Small- and medium-sized necrotising vasculitis may be implicated in the neurological complications of the disease.

Treatment

Treatment is usually with corticosteroids in high dose (prednisolone 40–60 mg daily); cytotoxics are rarely needed.

SARCOIDOSIS AND AUTOIMMUNE DISEASES

Sarcoidosis shares many features with the autoimmune connective tissue diseases with which it may be confused.⁷¹

Autoantibodies, particularly rheumatoid factor and antinuclear antibodies, may be found in low titre and may lead to the diagnostic confusion.

In addition, many case reports and small series of patients with proven sarcoidosis and a connective tissue disease have emerged^{72,73} which have raised the

question, 'Is sarcoidosis another autoimmune connective tissue disease?'

CONCLUSION

The musculoskeletal features of sarcoidosis may prove a diagnostic and therapeutic challenge to the rheumatologist. Many features of this multisystem disease, especially the chronic form, may mimic those found in the autoimmune connective tissue diseases. New therapeutic agents are available but have yet to be fully evaluated.

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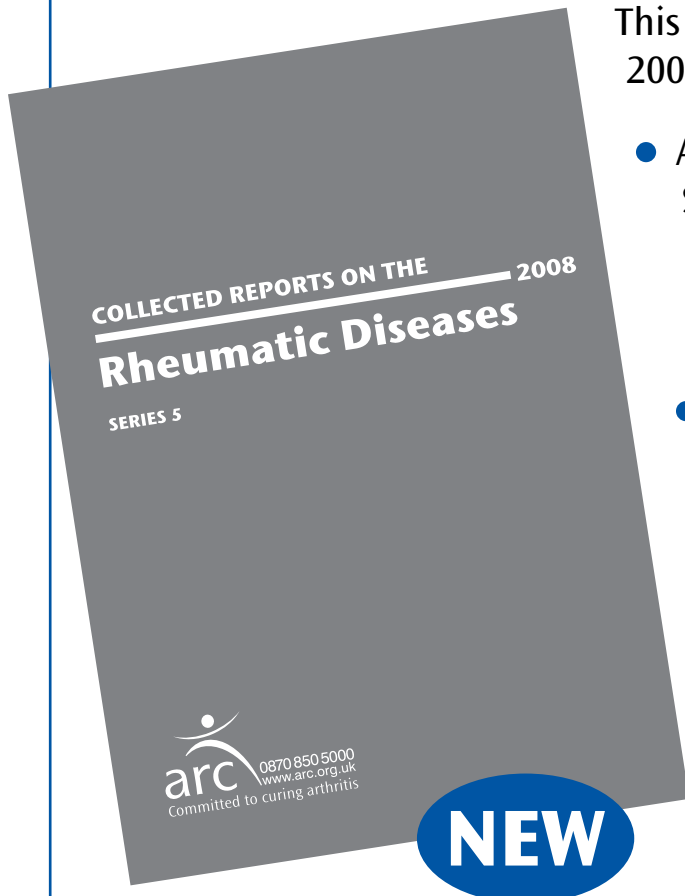
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