

Table 1**Stages of Pulmonary Involvement in Sarcoidosis**

Stage 1:	Bilateral hilar adenopathies without parenchymal involvement
Stage 2:	Bilateral hilar adenopathies plus pulmonary infiltrates
Stage 3:	Dense pulmonary infiltrates with lung insufficiency and/or <i>cor pulmonale</i> .

sent as different clinical syndromes involving the joints, periarticular soft tissues, muscles, and bones (1,2,5,7,13, 14,15).

Acute Arthritis

Acute additive, migratory arthritis may be the first manifestation of sarcoidosis. It can be oligoarticular or polyarticular, and only rarely is it monoarticular. The most commonly involved joints are the ankles, but it also may involve the knees, wrists, and elbows. Gran et al, in a study of 49 patients with acute sarcoidosis, found that 100% of the patients had ankle involvement; 41% had knee involvement; 33% had wrist involvement; and 20% had elbow involvement. Other joints, including the small joints of the hands and feet, the hips, and the sternoclavicular and sacroiliac joints were less frequently involved (16).

Swelling of the ankle region is frequently due to periarticular edema and tenosynovitis; true ankle effusions usually are not found (14,17,18).

Acute sarcoid arthritis is usually self-limited, and recurrences are uncommon. Symptoms last from just a few weeks to over 3 months (7,16). Destructive changes in involved joints are rare.

The acute arthritis is frequently associated with bilateral hilar adenopathy and erythema nodosum – a classical triad known as Lofgren’s syndrome. The association of acute arthritis and parenchymal lung involvement is less common (7,15,16).

Chronic Arthritis

Chronic arthritis is uncommon and is usually associated with long-standing sarcoidosis, particularly when skin manifestations also are present. It has been described mainly in African American

patients (5). The chronic arthritis associated with sarcoidosis is usually polyarticular and tends to involve the shoulders, hands, wrists, ankles, and knees. It is characterized by periods of remission, but it can be deforming. Dactylitis, similar to that seen in psoriatic arthritis, also may be noted, and a condition similar to Jaccoud’s arthropathy has been found in some patients (7).

Biopsy studies have shown noncaseating granulomas in the synovium as well as fibrosis and adhesions of the tendons and muscles surrounding the joints (7,14). Synovial fluid analyses have shown non-specific inflammatory changes with mononuclear and polymorphonuclear cells. Radiographic changes with cystic and destructive features have been observed in the phalanges of the hands (18) (Figure 1).

Myopathy

Sarcoid involvement of the muscles is usually asymptomatic. Noncaseating granulomas may appear in biopsies of clinically unaffected muscles. When myopathy is present, other organs are usually involved, and it is very seldom the initial manifestation of sarcoidosis (5).

Symptomatic muscle involvement with proximal weakness can occur, particularly in elderly women. Such involvement usually is insidious, symmetric, and involves the proximal muscles. Muscle atrophy is commonly seen. Electromyographic (EMG) studies show myopathic changes, but muscle enzymes may be normal (5,7,14).

An acute sarcoid myopathy – similar to polymyositis – is less commonly seen. It may involve elevated muscle enzymes and abnormalities as detected by EMG studies. The respiratory muscles also can be affected (5,7,14,19).

Nodular muscle involvement is rare, but

may present as a localized mass. Muscle weakness is usually absent. Characteristic changes appear on magnetic resonance images as well-demarcated lesions with star-shaped low-intensity signals in the center of the nodules.

Biopsies reveal granulomas with CD4 T-cells in the center and CD8 T-cells in the periphery. A random muscle biopsy may be a useful method for diagnosing sarcoidosis because there is evidence of muscle infiltration and granulomas in 75% to 100% of patients (5,7,14,19).

Bone Involvement

Osseous involvement, although sometimes painful, usually is asymptomatic. Lesions mainly occur on the hands and feet but can also affect the skull, ribs, sternum, vertebrae, nasal bones, pelvis, tibia, and femur. Bony lesions frequently are associated with chronic skin involvement and are present only in patients with long-standing sarcoidosis and multi-organ involvement. Radiographic changes show cystic and destructive lesions of the bone. Sclerosis and periosteal reactions typically

Figure 1 Hand roentgenogram

In this roentgenogram, cystic changes involve the bases of the middle phalanges of the middle and index fingers. Erosions are present in the first metacarpal head. The terminal tuft of the distal phalanx of the index finger shows loss of bone substance.

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are noted in the phalanges and metatarsal bones.

Nuclear studies with technetium 99 may help detect osseous involvement (5,7,14).

Sicca Symptoms

Sarcoidosis may involve the exocrine glands, including the salivary glands. There have been several reports of dry mouth and keratoconjunctivitis sicca in patients with sarcoidosis, which can make it difficult to clinically distinguish the condition from Sjögren's syndrome (20).

In a study conducted by Marx et al, minor salivary gland biopsies and parotid biopsies were performed when either radiographic evidence or clinical findings (eg, parotid swelling or sicca symptoms) suggested a patient had sarcoidosis. The biopsies revealed granulomatous changes in 36% of patients with sarcoidosis and sicca symptoms, whereas the same changes were present in 93% of the cases with parotid biopsies (21).

Laboratory Features

Liebermann reported in 1975 that patients with active pulmonary sarcoidosis had elevated angiotensin-converting enzyme (ACE) levels, whereas patients treated with glucocorticoids and patients with inactive disease had normal ACE levels (13). This enzyme is produced within the granulomas by epithelioid cells and alveolar macrophages through the release of an ACE-inducing factor. ACE is believed to affect the formation of granulomas by producing angiotensin-II locally, which in turn is chemotactic for macrophages and enhances phagocytosis (22).

Elevated ACE levels are present in 40% to 90% of patients, and because they often correlate with disease activity, checking ACE levels may be useful for monitoring response to therapy. Elevated ACE levels are not specific for sarcoidosis, however, and levels may be elevated in other conditions, including hyperthyroidism, liver cirrhosis, Gaucher's disease, and diabetes mellitus (13,22).

Hypercalcemia sometimes is noted in sarcoidosis. It is believed to be secondary to increased production of 1,25-dihydroxy-

vitamin D3 (calcitriol) by the activated macrophages present in the granulomas. The condition is usually transient and does not require treatment.

Treatment

Nonglucocorticoid anti-inflammatory drugs are used as initial therapy for patients with acute sarcoid arthritis. Patients with refractory disease, myopathy, chronic arthritis, or other organ involvement often require treatment with moderate doses of glucocorticoids (5). Patients with acute sarcoid myopathy respond well to glucocorticoids; an initial dosage of 1 mg/kg of prednisone (or equivalent dosage) is recommended.

Hydroxychloroquine may be used to treat patients with mucocutaneous disease. Taken concurrently with glucocorticoids, hydroxychloroquine also may be used to treat interstitial lung disease.

Chloroquine has been reported to be more effective than hydroxychloroquine, but it is associated with greater toxicity (23,24). Antimalarial agents also have been found to reduce hypercalcemia when treatment is necessary.

Colchicine has been reported to be helpful for patients with acute arthritis. Methotrexate should be considered in patients who respond poorly to glucocorticoids or who require high dosages for disease control. Carefully controlled studies of these agents, however, have yet to be conducted (5,24).

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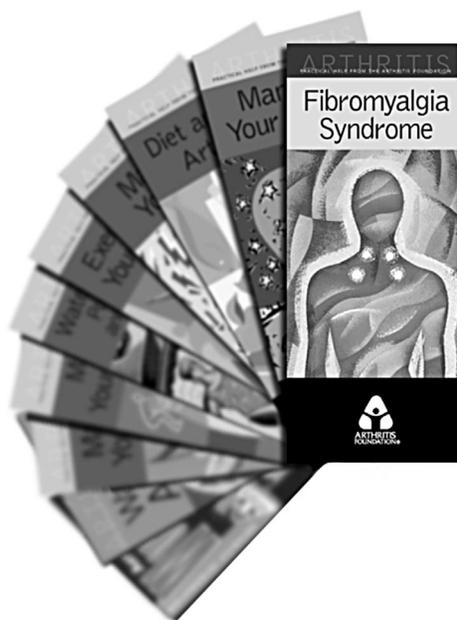
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SUMMARY POINTS

- Sarcoidosis is a chronic inflammatory condition characterized by the presence of noncaseating granulomas in the affected tissues.
- Pulmonary involvement is present in 90% of cases.
- Nonglucocorticoid anti-inflammatory drugs are used for initial therapy of acute sarcoid arthritis.
- Glucocorticoids usually are used for less responsive cases.

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Rheumatological Manifestations of Sarcoidosis

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Introduction

Sarcoidosis is a chronic inflammatory condition characterized by the presence of noncaseating granulomas in the affected tissues. The incidence of sarcoidosis is equal in both sexes, but sarcoidosis is predominant in African Americans and in people from Northern Europe (1,2). Disease onset usually occurs during early adulthood, but the onset of sarcoidosis can occur in children (3,4).

Etiology and Pathogenesis

The etiology of sarcoidosis remains unknown. A genetic predisposition to the disease has been described: HLA-DR5 has been reported in a subgroup of German patients, and patients with sarcoid acute arthritis have a higher prevalence of HLA-B8 and HLA-DR3 alleles (5,6).

Sarcoidosis has been associated with increased T-cell responses and decreased cellular immunity due to the observation of intense granulomatous formation along with frequent anergy to cutaneous antigens such as tuberculin, trichophyton, and mumps (2). The earliest immunologic event is often a CD4 T-cell alveolitis. Immunologic studies of biopsy material, infiltrates, and broncho-alveolar lavage have shown a predominance of T-helper cells and macrophages. Cytokine release from these T-cells may attract macrophages that in turn secrete IL-15 and stimulate T-cell growth

perpetuating the response. Leukotriene B4 is also secreted by macrophages and amplifies the granulomatous reaction by recruiting mononuclear phagocytes from the peripheral blood (7).

Clinical Picture

Pulmonary involvement is present in 90% of sarcoidosis cases, and the involvement has been described in 3 stages (Table 1). This globally accepted clinical staging was initially postulated in the 1960s (8,9).

Sarcoidosis often is self-limited, and patients who undergo spontaneous remissions usually do not relapse. In cases requiring glucocorticoid treatment, there is a high relapse rate after the glucocorticoid dose is tapered.

Erythema nodosum commonly occurs with sarcoidosis, particularly cases involving acute arthritis. Skin involvement is also relatively common, manifested by hyperpigmented papules in approximately 30% of cases.

Eye involvement, usually uveitis, is present in 20% of cases (10). Approximately 20% of patients with eye involvement become permanently blind. A study of 43 patients with sarcoid eye involvement found anterior uveitis as the initial presenting sign in 19% of cases. Of those studied, 47% had chronic anterior uveitis and 26% had acute anterior uveitis. Posterior uveitis was reported in 14% to 43% of the cases. Other eye manifestations included cataracts, glaucoma, synechiae, sicca, nodular lesions, and band keratopathy (11).

Peripheral nerve involvement, usually a seventh nerve palsy, also may occur with sarcoidosis (12).

Musculoskeletal Manifestations

Rheumatologic symptoms occur in 4% to 38% of patients with sarcoidosis and can pre-