CHAPTER 27

Sarcoidosis

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- Systemic inflammatory disorder with noncaseating granulomatous inflammation in affected organs, commonly involving the lungs, eyes, skin, joints, lymph nodes, and upper respiratory tract.
- Diagnosis attained via consensus between the clinical presentation and natural history, pattern of major organ involvement, confirmatory biopsy, and response to therapy.
- When treatment is indicated, glucocorticoids remain the only recognized effective therapy for active sarcoidosis.

Sarcoidosis is a systemic inflammatory disorder characterized by the presence of noncaseating granulomatous inflammation in affected organs (1). The etiology of sarcoidosis remains undetermined, the clinical manifestations of this disease are protean, and a diagnosis of sarcoidosis is often made by the exclusion of other processes. What helps distinguish sarcoidosis from other systemic disorders is a consideration of clinical presentation and natural history, confirmatory biopsy, and appropriate response to therapy. Although this disease most commonly affects the lungs, virtually any part of the body may be affected, and the presence and behavior of characteristic extrapulmonary manifestations may assist in supporting a diagnosis of sarcoidosis.

EPIDEMIOLOGY

The worldwide prevalence varies widely and has been reported to be 1 to 10 cases per 100,000 population in a diverse array of countries (Denmark, Belgium, Japan, Korea, Czechoslovakia). In Sweden, for reasons that are not clear, the prevalence is estimated to be between 60 to 80 per 100,000 (2,3). In the United States, the prevalence of sarcoidosis has been estimated to be 10 to 40 per 100,000. Studies using mass screening through chest radiography identify a significant number of asymptomatic patients with sarcoidosis (4,5). Other methods of case detection, for example, autopsy reports, generally conclude even higher rates of disease (6,7). Sarcoidosis tends to be diagnosed in younger adults (ages 20–40) although a second peak may be appreciated in Caucasian women over age 50. In the United States, the highest incidence of sarcoidosis is observed in young African-American women.

Genetic and Familial Associations in Sarcoidosis

Reports of families with more than one case of sarcoidosis support a genetic basis for this disease. The recently completed multicenter study in the United States—A Case Control Etiologic Study of Sarcoidosis (ACCESS)—estimated the relative risk for sarcoidosis to be approximately 5 among first-degree relatives of patients with sarcoidosis (8). In contrast to the higher annual incidence of sarcoidosis among African Americans (35.5 per 100,000) compared with Caucasians (10.9 per 100,000) (8), the relative risk of sarcoidosis among first-degree relatives of Caucasian patients may be substantially higher than that of first-degree relatives of African-American patients.

Many genetic associations have linked sarcoidosis with genes within the major histocompatibility complex (MHC) locus (9). Most recently, the novel gene BTNL2 (butyrophilinlike) (2) has been associated with sarcoidosis in a genomewide linkage analysis using a cohort of Caucasian patients (10). This finding was confirmed in a separate linkage analysis using a cohort of African-American patients from the Sarcoidosis Genetic Analysis (SAGA) consortium (11,12).

CLINICAL FEATURES

Sarcoidosis typically involves more than one organ. The frequency of involvement by organ system is shown in Table 27-1. Alternative diagnoses must always be excluded when considering rare and unusual presentations of sarcoidosis (13).

TABLE 27-1. CLINICAL FEATURES OF SARCOIDOSIS.

ORGAN SYSTEM	FREQUENCY OF CLINICALLY RELEVANT DISEASE (%)
Lung	70–90
Skin	20–30
Sinus and upper respiratory tract	5–10
Eye	20–30
Musculoskeletal	10–20
Abdominal	10–20
Hematological	20–30
Salivary/parotid	5–10
Cardiac	5–10
Neurological	5–10

Acute Sarcoidosis

Two acute presentations associated with eponyms are worth noting. First, Löfgren's syndrome consists of fever, erythema nodosum, bilateral hilar adenopathy, symmetric polyarthritis, and uveitis. Löfgren's syndrome is more common among Scandinavians. In most patients, the erythema nodosum and arthritis resolve after several weeks, often without specific therapy. Nonsteriodal anti-inflammatory drugs (NSAIDs) or low-dose glucocorticoids may be necessary in some patients. Once resolved, Löfgren's syndrome recurs in less than 30% of cases (14).

Second, lacrimal and salivary gland involvement causing glandular enlargement and the sicca syndrome may be a feature of an acute presentation of sarcoidosis, known as Heerfordt's syndrome ("uveoparotid fever"). Heerfordt's syndrome is a constellation of fever, granulomatous inflammation of the lacrimal and parotid glands, uveitis, bilateral hilar adenopathy, and cranial neuropathies.

Pulmonary Sarcoidosis

Lung involvement is detectable through chest radiographs in up to 90% of sarcoidosis patients. The most common symptoms include dyspnea and dry cough. Sputum production and hemoptysis are associated with fibrocystic pulmonary sarcoidosis and bronchiectasis. The physical examination is often unremarkable, with wheezes or crackles heard in less than 20% of patients.

A minority of patients may present with atypical chest pain. The etiology of this chest pain, which may occur either at rest or with activity, may be related to the presence of bulky mediastinal adenopathy. Most patients with mediastinal adenopathy, however, do not experience chest pain. The chest pain does not respond well to glucocorticoids, and the exclusion of cardiac, gastroesophageal, and musculoskeletal etiologies is important.

Pulmonary hypertension is a rare complication (<5%) of pulmonary sarcoidosis, usually found in patients with advanced lung disease (stage III or IV). Pulmonary hypertension is associated with higher rates of mortality. As with atypical chest pain, other potential contributors to pulmonary hypertension, for example, sleep apnea and thromboembolic disease, should be excluded.

Chronic Cutaneous Sarcoidosis

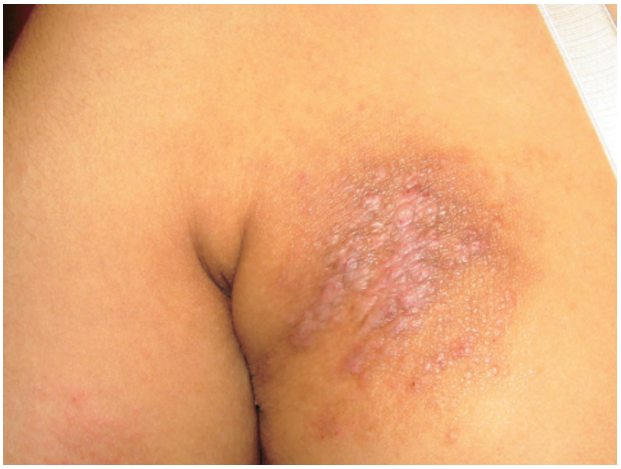
Skin lesions of various appearances may occur in up to one third of patients with sarcoidosis. The most common sarcoidosis skin lesions are hyperpigmented nodules, violaceous plaques, hypopigmented macules, and subcutaneous nodules (Figure 27-1). Such lesions most commonly occur over the extensor surfaces of the arms and legs and tend to resolve with scarring and retraction. *Lupus pernio*—a confusing name because the condition has nothing to do with systemic lupus erythematosus—refers to a particular type of sarcoidosis lesion that occurs on the face and scalp. Lupus pernio lesions (Figure 27-1) appear as violaceous plaques found on the nose, nasal alae, malar areas, eyelids, hairline, and scalp. They are indolent, but often difficult to treat.

Sinuses and Upper Respiratory Tract

Upper respiratory tract disease is common in sarcoidosis. Symptoms include severe nasal congestion and sinus pain. Hoarseness and stridor requires prompt evaluation by an otolaryngologist to document laryngeal involvement. A "saddle-nose deformity" may result from chronic disease or repeated surgical interventions. Mucocutaneous involvement is associated with other indolent manifestations, such as lupus pernio.

Ocular

A significant percentage of patients has ocular involvement. Nodular sarcoidosis lesions can involve all major compartments of the eye. Granulomatous conjunctivitis and conjunctival nodules are common findings that are sometimes accessible for biopsy. Intraocular sarcoidosis occurs more frequently in the anterior segment and can result in nodules on the pupillary margin, the surface of the iris, and the trabecular meshwork. Granulomatous



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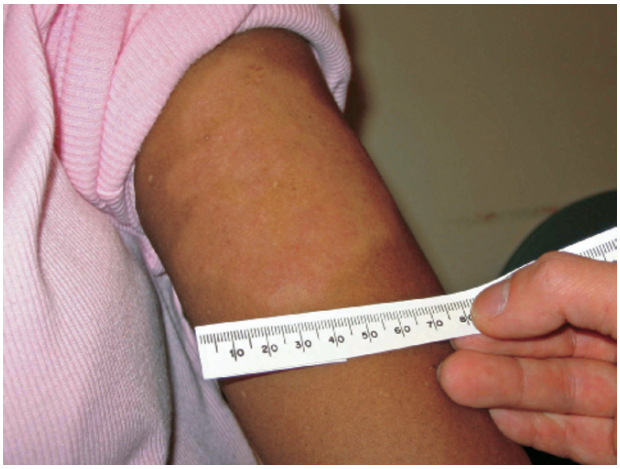

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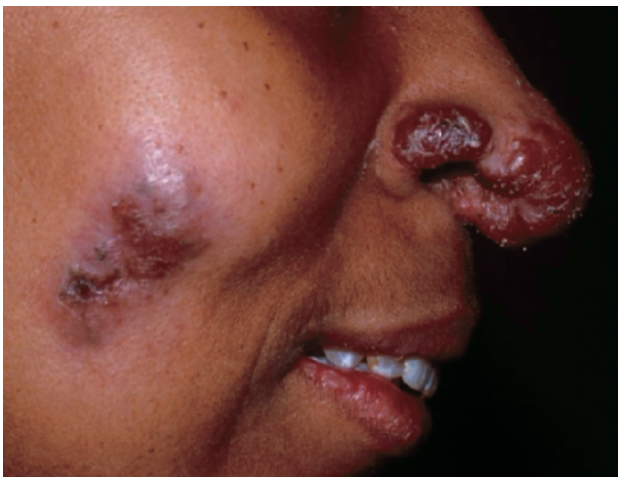

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FIGURE 27-1

Chronic cutaneous sarcoidosis. This manifestation of sarcoidosis can occur with a variety of appearances and include hyperpigmented nodular lesions (A) and hypopigmented macules (B). Cutaneous lesions most commonly occur over the extensor surfaces of the arms and legs and tend to resolve with scarring and retraction. Violaceous nodular lesions of lupus pernio are often indolent and more difficult to treat than other sarcoidosis skin lesions (C). (Figure 27-C, © Adrienne Rencioc, MD, PhD, © DermAtlas; http://www.DermAtlas.org.)

uveitis of the anterior chamber can lead to keratic precipitates on the posterior surface of the cornea which, on slit-lamp examination, have the appearance of "mutton-fat" droplets. Intermediate uveitis can lead to suspended "snowball" or "string of pearl" vitreous opacities, also characteristic of sarcoidosis. Posterior segment uveitis is often associated with superficial "candle wax" exudates and deeper chorioretinal lesions that may require fluorescein angiography for detection. Posterior uveitis can be associated with neurological involvement, that is, optic neuritis, in up to one quarter of cases, which may be difficult to distinguish from posterior uveitis. Both kinds of posterior eye involvement can result in abrupt blindness. Rare extraocular manifestations include involvement of the lacrimal gland, tear duct system (dacrocystitis), ocular orbit (often unilateral), cornea, and scleritis. The range and potentially insidious nature of ocular findings in sarcoidosis make regular ophthalmologic evaluations an important part of care.

Musculoskeletal

Joint

As noted, frank arthritis tends to occur in patients with acute presentations of sarcoidosis (Löfgren syndrome). Arthralgias occur commonly in patients with chronic active sarcoidosis. Chronic sarcoid arthritis is a rare manifestation (<1%) that can result in joint deformities, and is associated with other chronic manifestations such as cutaneous sarcoidosis (15). Arthrocentesis reveals mild elevations in white blood cell counts (250–5000/mL) with a mononuclear cell predominance. Synovial biopsy may reveal noncaseating granulomatous inflammation. Frank tenosynovitis and periarticular inflammation occur less frequently than arthralgias or arthritis, but periarthritis (inflammation around a joint rather than in it, sometimes difficult to discern from true synovitis) is well described in sarcoidosis. Other articular manifestations of sarcoidosis would include dactylitis, characterized by a violaceous swelling involving the

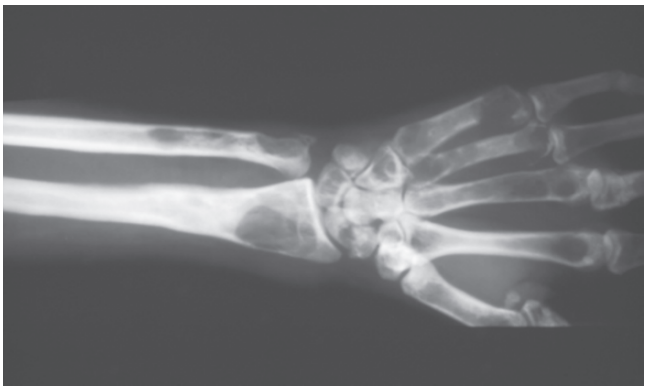


FIGURE 27-2

Osseous sarcoidosis. A 45-year-old woman with a 2- to 3-year history of cough, fevers, exertional dyspnea, and recurrent swelling and stiffness in both hands. A diagnosis of sarcoidosis was established by bronchoscopy. This plain film of the hand reveals multiple punched-out lesions that are characteristic of osseous sarcoidosis. (Johns Hopkins Arthritis Website, http://www.hopkins-arthritis.org., S. Levine, MD and W. Scott, MD.)

second or third fingers, sacroiliitis, and bilateral heel pain.

Bone

Cystic, punched-out lesions and lacey reticulations are commonly observed on plain radiographs or other imaging studies, often as incidental findings (Figure 27-2). Such lesions, typically located in the bones of the hands and feet, can also be found in the skull and vertebrae. Lesions involving the pelvis may be associated with pain that mimics sacroiliitis (16). Bone biopsies may be necessary in osseous sarcoidosis to exclude infections or cancers that may result in similar radiographic findings.

Myositis

Random muscle biopsies may reveal granulomas in 50% to 80% of cases, but muscle involvement in sarcoidosis is often asymptomatic. Muscle inflammation can also be detected incidentally by radiographic imaging using gallium scanning and magnetic resonance imaging (MRI). Glucocorticoid-induced myopathy should be considered in patients who develop acute-onset weakness following the initiation of treatment.

Abdominal

Granulomatous inflammation may be detected in more than 50% of liver biopsies in sarcoidosis, but clinically significant liver disease is present in not more than 10% of all cases. Elevated liver enzymes often resolve spontaneously or with therapy with glucocorticoids. Chronic granulomatous hepatitis may progress to cirrhosis, however, particularly if severe and left untreated (17). The constellation of hepatosplenomegaly, abdominal adenopathy, hepatosplenomegaly, and hypercalcemia (and often bone marrow involvement) is often referred to as *abdominal sarcoidosis*.

Involvement of the gastrointestinal tract is rare. It is often associated with pain and dysmotility and does not respond well to glucocorticoids. In patients where this is the sole or principal manifestation of sarcoidosis, then other causes of inflammatory bowel disease (Crohn's disease, ulcerative colitis) should be excluded.

Other Important Manifestations

A wide range of hematological manifestations may be found in up to one third of patients with sarcoidosis (18). Peripheral adenopathy occurs commonly at time of disease presentation, and bulky adenopathy may persist in ~10% of cases. Massive splenomegaly may be present in 5% of cases. Anemia, lymphopenia, and leucopenia may be observed in 30% to 50% of all cases and is more common than thrombocytopenia. A polyclonal gammopathy is also frequently seen (~25%) in many patients with active sarcoidosis. Common variable immunodeficiency (CVID) should be suspected in patients who lack elevations in serum globulin fraction or develop an increased frequency of infections, both of which are unusual in sarcoidosis (19).

Cardiac sarcoidosis is a rare but important manifestation that can lead to heart block, malignant arrhythmias, and cardiomyopathy. Autopsy series suggest that the incidence of cardiac sarcoidosis may be as high as 25%, but clinical diagnoses of this condition are made in <10% of patients. Endomyocardial biopsy detects granulomatous inflammation in less than 25% of cases (20). The diagnosis is frequently rendered indirectly in a patient with biopsy-proven sarcoidosis at other sites and a compatible myocardial imaging study, such as nuclear medicine stress test, cardiac MRI with gadolinium contrast, or positron emission tomography (PET).

Presentations of neurosarcoidosis can be placed into three major groups. The most common form would be neuropathies involving cranial nerves II (optic neuritis), V, VII, IX, or XII. Cranial neuropathies, usually associated with an aseptic basilar meningitis, tend to recur intermittently. A second presentation of neurosarcoidosis is encephalopathy or myelopathy associated with either a mass or an enhancing lesion on MRI. Such patients benefit from prolonged courses of immunosuppression. Finally, the third presentation of neurosarcoidosis is peripheral neuropathy. This complication is potentially disabling and often unresponsive to glucocorticoids. A small fiber neuropathy has been implicated recently as a significant cause of chronic pain and fatigue in sarcoidosis (21).

RADIOGRAPHIC FEATURES

Chest radiographs detect abnormalities in ~ 90% of all patients with sarcoidosis (22). Chest radiograph abnormalities are assigned a category (stage) according to the Scadding system: 0, normal; I, bilateral hilar lymphadenopathy (BHL); II, BHL + interstitial infiltrates; III, interstitial infiltrates only; IV, fibrocystic lung disease (Figure 27-3). Computed tomography scans of the chest reveal that the pulmonary infiltrates of sarcoidosis are typically nodular in appearance, and tend to distribute themselves along bronchovascular structures (Figure 27-4).

The presence of inflammation suggesting active sarcoidosis can be identified in the brain, cranial nerves, spinal cord, heart, or other soft tissue organs using MRI with gadolinium contrast or PET scanning. Cardiac sarcoidosis can also be inferred from gated thallium scanning. Classic findings associated with sarcoidosis revealed by 67-gallium scanning include uptake in the parotid and lacrimal glands ("panda sign") and uptake in bilateral hilar and right paratracheal lymph nodes ("lambda sign"). Although these radiographic findings are highly typical of sarcoidosis, a biopsy is still required to confirm diagnosis.

LABORATORY FEATURES

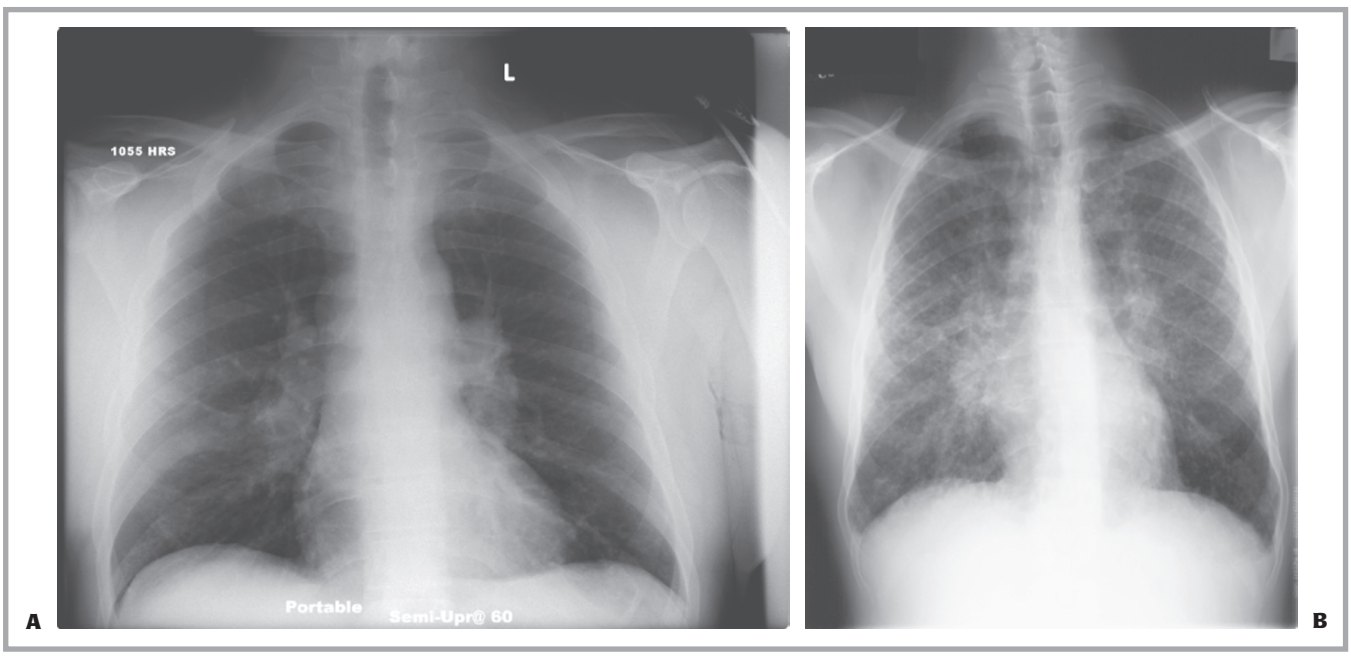
Routine bloodwork consisting of comprehensive metabolic panel and complete blood count is useful to screen for abnormalities (renal function, kidney function, anemia, lymphopenia, hypercalcemia, hypergammaglobulinemia) associated with extrapulmonary sarcoidosis. No biomarkers are useful in predicting outcomes or guiding treatment decisions. Serum levels of angiotensin-converting enzyme and the active form of vitamin D (1,25-dihydroxy vitamin D_3) are elevated in some patients with active sarcoidosis, but these test results have poor specificity and little utility in either the diagnosis or management of sarcoidosis (23).

PATHOLOGY

Sarcoidosis is associated with well-formed epithelioid granulomas in the absence of other known causes of granulomatous disease, such as infection and malignancy. These granulomas are typically noncaseating, although fibrinoid necrosis can occasionally be seen. In the lung, the granulomas tend to occur along bronchovascular structures.

FIGURE 27-3

Pulmonary sarcoidosis (A, B). Chest radiograph (A) compatible with Scadding stage I, demonstrating bilateral hilar and right paratracheal adenopathy without significant parenchymal infiltrates. This patient presented with constitutional symptoms (fevers, unintentional weight loss), arthralgias, and a cough. A transbronchial biopsy revealed noncaseating granulomatous inflammation. In another patient (B), the presence of both adenopathy and pulmonary infiltrates signifies a Scadding stage III radiograph.



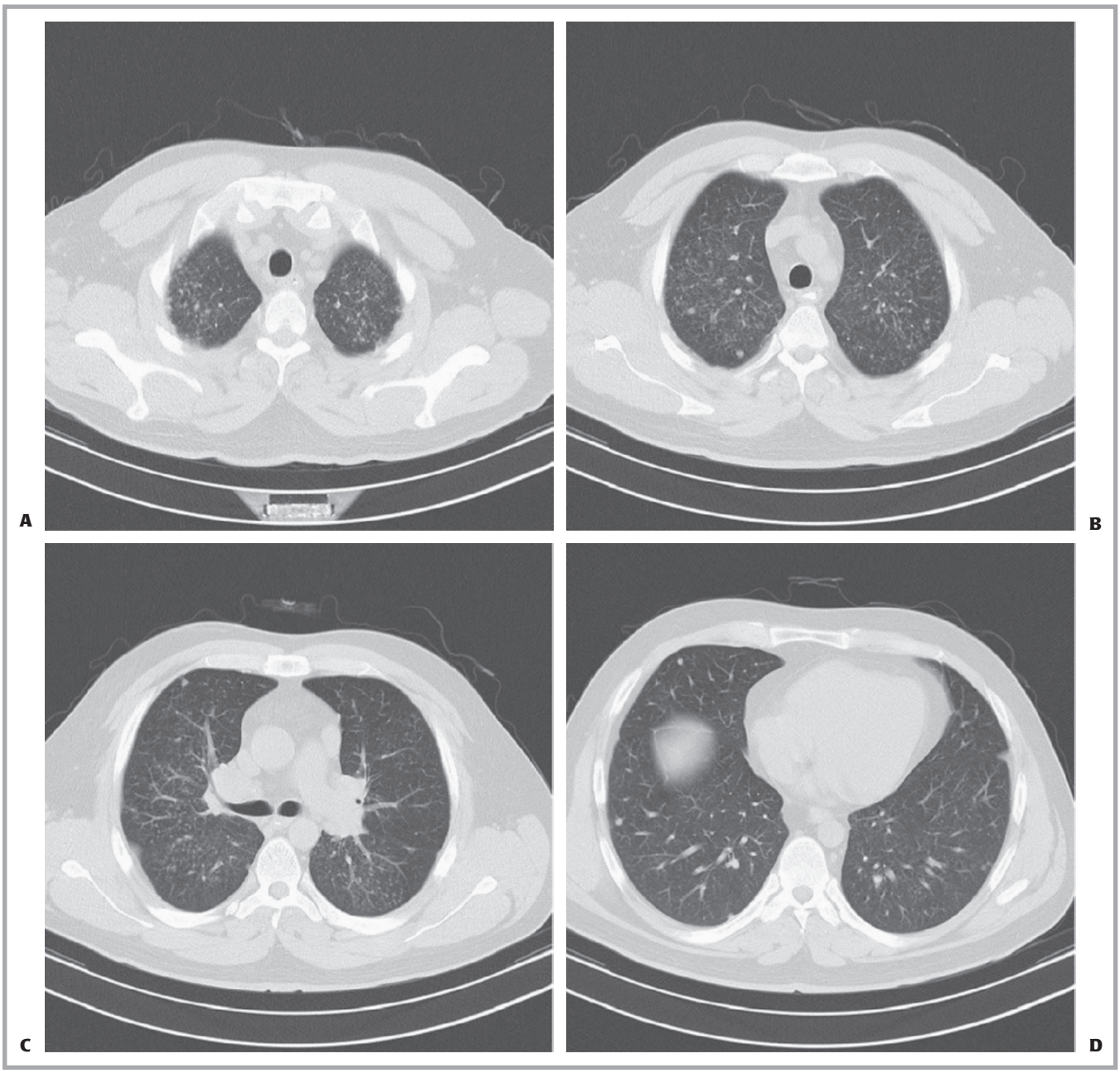


FIGURE 27-4

(A–C) Pulmonary sarcoidosis. Computed tomography scans of the chest, revealing patchy, diffuse reticulonodular infiltrates predominantly involving the upper and middle lung fields with a bronchovascular distribution. If observed on a chest radiograph, such findings would be comparable with a Scadding stage II (Scadding stages are based upon radiographs, not computed tomography scans).

PATHOGENESIS

The cause of sarcoidosis remains uncertain. The active granulomatous inflammation of sarcoidosis is associated with a dominant expression of T-helper (Th)1 cytokines [interferon gamma (IFN-gamma), interleukin (IL)-12, IL-18] and tumor necrosis factor (TNF) (24). Oligoclonal expansion of T cells bearing a limited set of T-cell receptors in the lung, skin, and other sites of disease support the hypothesis that sarcoidosis involves an antigen-driven response (25). The most compelling example of this is the over-representation of T cells bearing the V alpha 2.3 T-cell receptor subunit reported in a significant portion of Scandinavian patients (26).

One prevailing hypothesis is that an exposure, possibly of microbial origin, triggers the development of sarcoidosis. Recent laboratory studies suggest that sarcoidosis may be associated with a previous exposure to microbial antigens (27,28), although sarcoidosis does not represent an active infection. The large multicenter ACCESS study failed to identify a dominant environmental or occupational exposure associated with an increased risk for developing sarcoidosis (29).

TREATMENT

Clinical Course and Prognosis

Nearly all patients with sarcoidosis experience one of two clinical courses: (1) sustained clinical remission or (2) chronic active disease that does not remit. Thus, sarcoidosis differs from many rheumatological diseases in that waxing and waning courses with intermittent flares and remissions are unusual. The major exception to this rule is the neurosarcoidosis presentation of optic neuritis and cranial neuropathies, which may recur several years after apparent remission.

Most patients who achieve remission do so within the first 2 to 3 years of diagnosis. Acute sarcoidosis (Löfgren syndrome) is associated with a high rate of remission (>70%). Unremitting, chronic active disease is associated with a greater burden of lung disease (stage III or IV), sinus and upper respiratory tract involvement, lupus pernio, neurosarcoidosis, cardiac involvement—organ system manifestations characterized by indolent presentations. Careful follow-up for at least several years (>2–3) is necessary to confirm whether a patient has remitting or chronic active sarcoidosis. Long-term follow-up is also important to ensure that patients with chronic active disease receive adequate treatment to minimize progressive impairment of organ function from chronic inflammation.

Although sarcoidosis is a systemic disorder, the extent of organ involvement is largely defined at presentation. The recent ACCESS study found that less than 25% of patients developed new organ involvement within 2 years of follow-up (30).

Therapy

The first step in deciding upon a treatment course is to exclude the presence of immediately life-threatening disease manifestations. In patients with limited cutaneous disease or the Löfgren syndrome, NSAIDs may be sufficient to control symptoms. Local steroid injections may be considered for isolated skin lesions. Patients with critical organ involvement (heart, central nervous system) should be treated aggressively with high doses of systemic glucocorticoids. In all cases, the selection of tangible endpoints (pulmonary function tests, chest radiograph, bloodwork, MRI studies) rather than subjective symptoms (fatigue, cough, localized pain) is essential to good therapeutic decision making. Although sarcoidosis is often considered a restrictive lung disease (low forced vital capacity or total lung capacity), changes in airway obstruction (FEV_1) and/or diffusion capacity (DLCO) may herald clinical deterioration in some patients with lung involvement.

For patients who require systemic therapy, glucocorticoids remain the only uniformly effective medication for active inflammation. Topical glucocorticoids (inhaled, ointment) are ineffective except for some instances of ocular involvement. In general, patients should be treated for an initial period of 8 to 12 months before attempting to discontinue glucocorticoids (tapering of the daily dose to a tolerable level, however, is essential). Patients with Löfgren syndrome generally have a good prognosis and earlier attempts to curtail systemic glucocorticoids can be considered. Patients who have chronic active disease should be treated with a stable maintenance regimen of low-dose glucocorticoids rather than repeated aggressive tapering regimens on and off glucocorticoids. End-stage changes (scarring) are not amenable to any treatment. Most patients demonstrate a lower limit for prednisone dosing, below which their disease will flare.

Untreated patients initially require higher doses of glucocorticoids (prednisone 20–40 mg/day) to control active disease, which can be tapered gradually after the first month, by 5-mg intervals every 2 weeks down to 20 mg/day, then more gradually below this dose with smaller increments (2.5 mg) and longer intervals (1–2 months). If symptoms recur or pulmonary function deteriorates with interval dose reduction, the patient should resume the previously effective dose of prednisone and the addition of a steroid-sparing agent should be considered. The average maintenance dose of sarcoidosis for most patients tends to be 5 to 15 mg/day. Patients with neurosarcoidosis or cardiac sarcoidosis may benefit from even higher doses of glucocorticoids in combination with steroid-sparing immunosuppressants.

Steroid-Sparing Agents

A variety of steroid-sparing immunosuppressants and immunomodulating agents are recommended to help minimize the maintenance dose of glucocorticoids (ideally $\leq$15 mg/day). However, most potential steroid-sparing agents have not been tested rigorously in randomized clinical trials. In contrast to glucocorticoids, which induce responses within several days to a few weeks, steroid-sparing agents may require a few months of therapy (2–6) before any clinical benefit is evident.

Antimalarial drugs (hydroxychloroquine, chloroquine) and synthetic tetracyclines (minocycline, doxycy-

cline), medications with few serious side effects, are used primarily to help control mucocutaneous disease. Pentoxifylline and thalidomide may be useful in a small subset of patients, but may have more significant side effects. Other immunosuppressive agents (methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide) have been used in conjunction with glucocorticoids to treat more severe manifestations of sarcoidosis that cannot be managed with lower doses of glucocorticoids alone or when intolerable glucocorticoid-related side effects occur. A recently completed phase II trial demonstrated that patients treated with infliximab, a monoclonal antibody targeted against TNF, experienced mild improvement in pulmonary function (31). Etanercept, a soluble TNF inhibitor, was shown to be ineffective in a randomized clinical trial (32). Further evaluation is necessary to determine the role of anti-TNF agents such as infliximab (and an analogous agent, adalimumab) in the treatment of sarcoidosis.

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