

SARCOIDOSIS

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues. Etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ. Pulmonary symptoms range from none to exertional dyspnea and, rarely, lung or other organ failure. Diagnosis usually is first suspected because of pulmonary involvement and is confirmed by chest x-ray, biopsy, and exclusion of other causes of granulomatous inflammation. First-line treatment is corticosteroids. Prognosis is excellent for limited disease but poor for more advanced disease.

Sarcoidosis most commonly affects people aged 20 to 40 but occasionally affects children and older adults. Sarcoidosis is more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Pathogenesis and morphology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T cells and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition.

The inflammatory process leads to formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that differentiate into epithelioid and multinucleated giant cells and are surrounded by lymphocytes, plasma cells, fibroblasts, and collagen. Granulomas occur most commonly in the lungs and lymph nodes but can involve any organ and cause significant dysfunction. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Hypercalcemia may occur because of increased conversion of vitamin D to the activated form by activated macrophages. Hypercalciuria may be present, even in patients with normal serum calcium levels. Nephrolithiasis and nephrocalcinosis may occur, sometimes leading to chronic kidney disease.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90% of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise, weakness, anorexia, weight loss, and low-grade fever are also common. Sarcoidosis can manifest as fever of unknown origin. Systemic involvement causes various symptoms (ankle, knee, wrist, and elbow arthritis erythema nodosum, perifericial adenopathy, ocular symptoms, lymphocytopenia, anemia due to granulomatous infiltration of bone marrow, sometimes causing pancytopenia, splenic sequestration causing thrombocytopenia, etc.)

Löfgren syndrome.

Löfgren syndrome manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It often causes fever, malaise, and uveitis, and sometimes

parotitis. Löfgren syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Heerfordt syndrome.

Heerfordt syndrome (uveoparotid fever) manifests as swelling of the parotid gland (due to sarcoid infiltration), uveitis, chronic fever, and less often palsy of the facial nerve. Heerfordt syndrome can be self-limited.

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. Bilateral hilar adenopathy is the most common abnormality. If sarcoidosis is suspected, a chest X-ray should be the first test if it has not already been done. The X-ray appearance tends to roughly predict the likelihood of spontaneous remission. in patients with only thoracic lymph node involvement. However, staging sarcoidosis by chest X-ray can be misleading; for example, extrapulmonary sarcoidosis, such as cardiac or neurologic sarcoidosis, can portend a poor prognosis in the absence of pulmonary involvement. Also, chest X-rays findings predict pulmonary function poorly, so that chest x-ray appearance may not accurately indicate the severity of pulmonary sarcoidosis.

Chest X-ray Staging of Sarcoidosis

Stage 0 - Normal chest x-ray

Stage I - Bilateral hilar, paratracheal, and mediastinal lymphadenopathy without parenchymal infiltrates

Stage II - Bilateral hilar and mediastinal adenopathy with interstitial infiltrates (usually in upper lung fields)

Stage III - Diffuse interstitial infiltrates without hilar adenopathy

Stage IV - Diffuse fibrosis, often associated with fibrotic-appearing conglomerate masses, traction bronchiectasis, and traction cysts

A normal chest x-ray (stage 0) does not exclude the diagnosis of sarcoidosis, particularly when cardiac or neurologic involvement is suspected. A high-resolution CT is more sensitive for detecting hilar and mediastinal lymphadenopathy and parenchymal abnormalities. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls, beading of the interlobular septa, ground-glass opacification, parenchymal nodules, cysts, or cavities, bronchiectasis.

Sarcoidosis is to be differentiated from TB, atypical Mycobacterial infection, fungal infection, Hodgkin lymphoma and non-Hodgkin lymphoma and some other diseases. Exclusion of other diagnoses is critical, especially when symptoms and X-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation.

Biopsy confirmation

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease. Peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible.

Löfgren syndrome does not require confirmation by biopsy.

Endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal or hilar lymph node is usually the diagnostic procedure of choice in

patients with intrathoracic involvement. Bronchoscopic transbronchial biopsy can be tried when endobronchial is nondiagnostic. If bronchoscopy cannot be tolerated, mediastinoscopy can be done to biopsy mediastinal or hilar lymph nodes, or video-assisted thoracoscopic lung biopsy or open-lung biopsy can be done to obtain lung tissue.

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DLco) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured at rest but may show effort desaturation in patients with more extensive lung involvement.

Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum calcium should be measured to detect hypercalcemia. Elevated ESR is common but nonspecific. Measurement of calcium in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum calcium levels.

BAL is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes >10%), a CD4+/CD8+ ratio of > 3.5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

PET scanning may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal, parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

Prognosis

Although spontaneous remission is common, disease manifestations and severity are highly variable, and many patients require corticosteroids at some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90% of patients who have spontaneous remission, remission occurs within the first 2 yr after diagnosis; < 10% of these patients have relapses after 2 yr. Patients who do not experience remission within 2 yr are likely to have chronic disease.

Prognosis is worse for patients with extrapulmonary sarcoidosis.

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

Treatment includes NSAIDs, corticosteroids and occasionally immunosuppressants.

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial X-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (routine renal and liver function testing, annual ophthalmologic examination). The frequency of follow-up testing is determined by the severity of disease.

Patients who require treatment regardless of stage include those with the following: worsening symptoms, limitation of activity, markedly abnormal or deteriorating lung function, worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension), heart, nervous system, or eye involvement, renal or hepatic insufficiency or failure, moderate to severe hypercalcemia, disfiguring skin or joint disease

NSAIDs can be used to manage symptoms.

The presence of chest imagining abnormalities without significant symptoms or evidence of decline in organ function is not an indication for treatment.

Therapy with corticosteroids

A standard protocol is prednisone 20 mg to 40 mg po once/day, depending on symptoms and severity of findings. Alternate-day regimens may be used: eg, prednisone 40 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in neurologic disease. Response usually occurs within 6 to 12 weeks, so symptoms and pulmonary function tests may be reassessed between 6 and 12 weeks. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (prednisone 10 to 15 mg/day) after evidence of response and are continued for a minimum of 6 to 12 mo if improvement occurs.

The optimal duration of treatment is 8-10 months. Premature taper can result in relapse. The drug is slowly stopped if response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50% of the time, monitoring should be repeated, usually every 3 to 6 months.

Inhaled corticosteroids can relieve cough in patients with endobronchial involvement or with hyperreactive airways.

Topical corticosteroids may be useful in dermatologic, nasal sinus, and ocular disease.

Immunosuppressants.

About 10% of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate 10 to 15 mg per week. Initially, methotrexate and corticosteroids are both given; over 6 week to 8 week, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 months. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 weeks initially and then every 4 to 6 weeks once a stable dose is achieved. Folate (1 mg po once/day) is recommended for patients treated with methotrexate. Other drugs reported to be effective in small numbers of patients who are corticosteroid-resistant or who experience complicating adverse effects include azathioprine, mycophenolate, cyclophosphamide.

No available drugs have consistently prevented pulmonary fibrosis.

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