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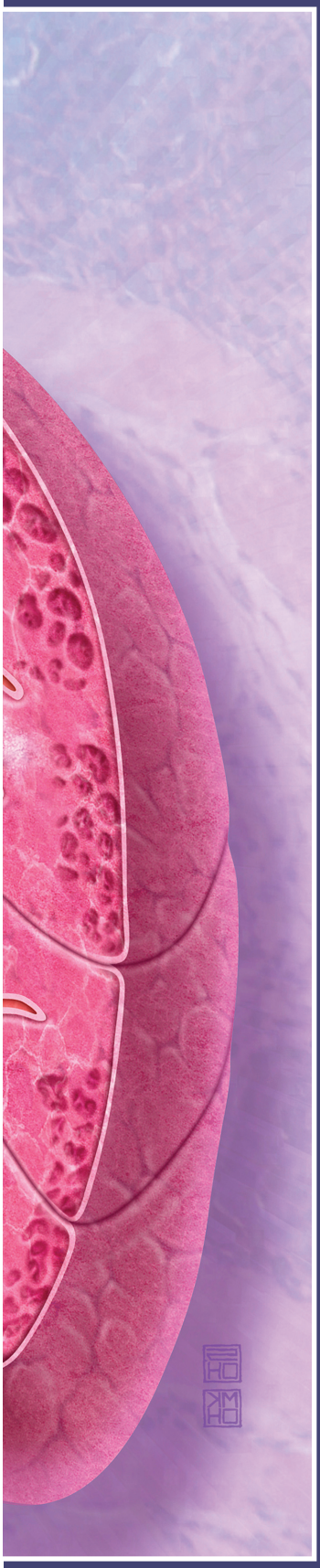


Sarcoidosis

A granular view

By Laura LaRue, MSN, FNP-BC

Sarcoidosis is a systemic disease that causes inflammation of body tissues and systems, leading to the deposition of abnormal epithelioid cells that form noncaseating granulomas. Ongoing research has improved clinical assessment, immunological, and genetic-testing methods, but the exact mechanism of how the different factors work together to cause the disease is still not understood. It affects women more than men, and in some cases may be caused by genetic influences or racial makeup.[1]

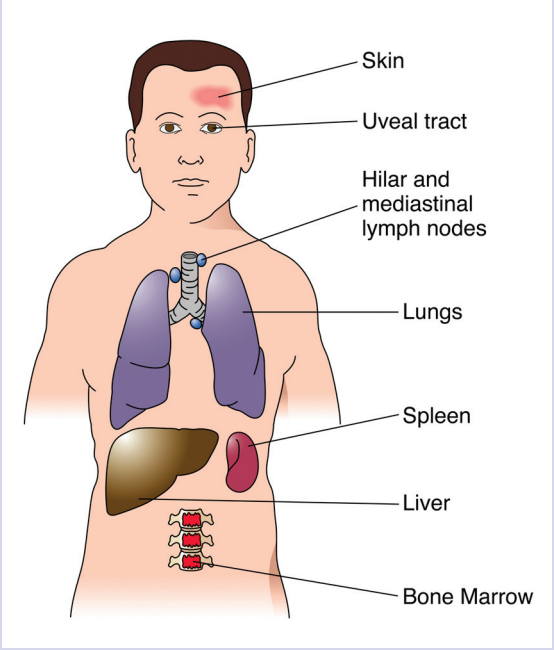
Sarcoidosis may be isolated to a particular organ system, or it may affect multiple organ systems. It is not considered a communicable disease. Often, the disease is asymptomatic and self-limiting, and can be difficult to diagnose initially. In severe cases, it can be life-threatening with progression to organ failure.

The disease

Sarcoidosis is a multisystem disease in which there is an abnormal immune response to inflammation by deposition of abnormal cells. The immune system is disrupted by inconsistent activation and depression. It isolates certain areas and deposits microscopic inflammatory epithelioid cells that form the characteristic granulomas without caseation (some may have fibrinoid at the center). Cells

Organs commonly affected by sarcoidosis

Sarcoidosis involves several organs; the most common are the lungs and lymph nodes.



Source: Rubin R, Strayer D, eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:526.

Genetic link to sarcoidosis

There is a clustering of the disease within families, with an increase of concordance in monozygotic twins over other siblings. Siblings have a fivefold increased risk of developing sarcoidosis. Meta-analysis, using an age-sex database and other variables, reveals that race is a reliable predictive factor for risk and presentation.[5–7] A case-control etiologic study of sarcoidosis did not identify one single cause or gene, but through genome scans, researchers found a link to chromosome 5 in African-Americans and to chromosome 6 in those of German descent.[2]

with a fibrinoid center form hyaline fibrous tissue that may lead to fibrosis.[2] As the numbers of granulomas increase and fibrosis occurs, organ function decreases. The disease affects the following organ systems, with the highest rate listed first: lungs; lymph nodes, especially in the chest; liver; skin; cardiac system; nervous system; renal system; and eyes (see *Organs commonly affected by sarcoidosis*). The exact cause is unknown, but it is generally accepted that genetics cause susceptibility to immune system changes triggered by environmental, occupational, chemical, or infectious agents. The immune system prompts the T-helper lymphocytes, which respond in an exaggerated manner and trigger the formation of granulomas.[3] Granulomas can dissolve, but may cause scarring or fibrosis, which affects the function of the involved organ.

Sarcoidosis affects all races, all ages, and both sexes. Its global incidence is 16.5 per 100,000 men, and 19 per 100,000 women.[1] In whites, it occurs in 10.9 per 100,000 population and is more likely to be asymptomatic. There is an increased risk in African-Americans, with 35.5 per 100,000 population and two times more likely in women than men.[4] African-Americans are more likely to have skin problems, along with more severe and disseminated sarcoidosis (see *Genetic link to sarcoidosis*). The skin problems are not erythema nodosum, but a more chronic granuloma known as lupus pernio. There is a higher occurrence of sarcoidosis in those younger than 40, with a peak age between 20 and 29, and a second peak in women older than 50.[4] There is also an increased incidence in northern European countries: 60 per 100,000 people in Sweden and Iceland. Japan has a higher incidence, especially in cardiac sarcoidosis. Other countries report a lower occurrence, which may be due to a lack of screening programs or the presence of other granulomatous diseases such as tuberculosis.

Clinical presentation

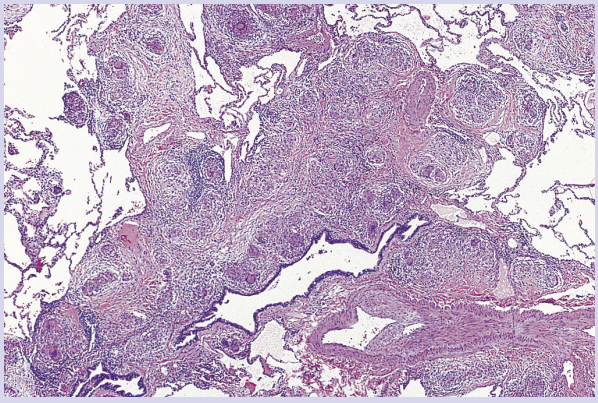
Some patients do not present with any symptoms, and the disease is identified by chance through a chest X-ray or other testing. More than 90% of all cases include pulmonary involvement.[8–10] Pulmonary sarcoidosis is characterized by central hilar lymphadenopathy and granulomas.[7] Symptoms include dry cough, dyspnea, night sweats, weight loss, fatigue, chest pain, and shortness of breath occurring with activity or speech. Necrotizing granulomas cause pulmonary fibrosis that decrease lung volume and expansion. Between 20% to 30% of affected patients sustain permanent lung damage, and untreated pulmonary sarcoidosis can lead to cardiac sarcoidosis.[10] Cardiac sarcoidosis may cause symptoms similar to those of heart failure, pulmonary hypertension, syncope or peripheral edema, cardiac dysrhythmia, electrical conduction disturbances, cardiomyopathy, and pericardial effusion.[4,11]

Lymph nodes are the second most affected, especially in the chest. The nervous system is affected in 10% to 15% of all cases; one-half of these affect the central nervous system, and 20% experience seizures.[10] Neurosarcoidosis affecting the seventh cranial nerve causes Bell's palsy in 25% to 50% of cases. Other presentations include hydrocephalus, headaches, gait disturbances, and elevated intracranial pressure.[7]

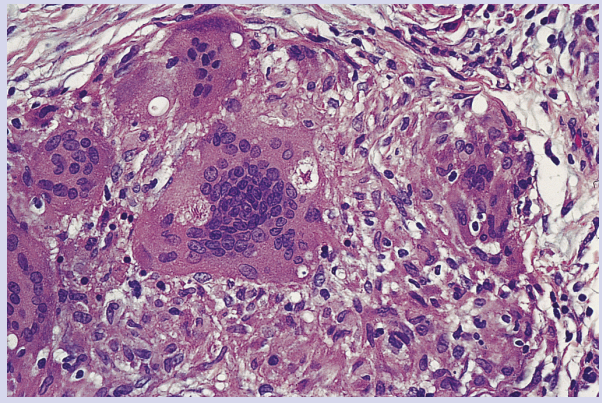
Noncaseating granulomas in sarcoidosis

The histologic illustrations of sarcoidosis below show multiple noncaseating granulomas present along the bronchovascular interstitium **(A)** and noncaseating granulomas that consist of tight clusters of epithelioid macrophages and multinucleated giant cells. **(B)**

(A)



(B)



Source: Rubin R, Strayer D, eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:527.

Skin involvement is marked by sarcoid granulomas found on the extremities and face. They are similar in appearance to erythema nodosum that occurs at the onset of other forms of sarcoidosis.[8] The nodules may be warm and tender and are more common in men and whites, but are transient. The sarcoid granulomas are distinguishable from erythema nodosum histological. Lupus pernio are purplish-red nodules that occur on the face, hands, and feet.[7] Lofgren's syndrome is associated with a relatively good prognosis and consists of fever, enlarged lymph nodes, arthritis (especially in ankles and more common in men and whites), or erythema nodosum. Erythema nodosum, more common in whites, are reddish or reddish-purple papules on ankles and other extremities, which may be warm or tender.[11]

The first indication of ocular involvement may be red, swollen, or watery eyes, which are common symptoms in children. There may be visual changes because of corneal involvement, uveitis, photophobia, and conjunctivitis. These can lead to cataracts, glaucoma, and optic nerve involvement with possible blindness.[7,10]

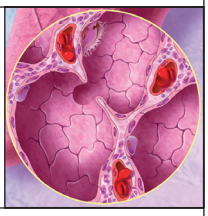
The gastric system can be affected, but symptoms are rare.[12]

Diagnosis

Diagnosis begins with a complete medical, family, and social history followed by a complete physical exam. A chest X-ray can often lead to early diagnosis by showing hilar lymphadenopathy, granulomas, or fibrosis. Identification of stages I through IV is indicated by the presence of granulomas and fibrosis. Changes in chest X-ray may rule out other differential diagnoses with similar symptoms. Some differential diagnoses include berylliosis from exposure to beryllium, tuberculosis, farmer's lung, hypersensitivity pneumonitis, fungal infection, rheumatoid arthritis (RA), rheumatic fever, and lymphoma.

Lab tests may indicate hypercalcemia or hypercalciuria, and liver function studies may be elevated. In women, thyroid function may be abnormal. Angiotensin-converting enzyme (ACE) levels are not as reliable because they can indicate other illnesses, but they are elevated in 40% to 90% of sarcoidosis patients, as granulomas secrete large amounts of ACE.[8] Sarcoidosis affects intrathoracic lymph nodes in more than 90% of cases.[13]

Sarcoidosis is often asymptomatic and self-limiting, making it difficult to diagnose initially.



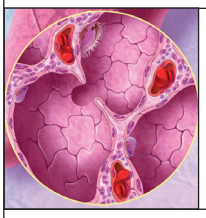
Computed tomography of the chest may reveal interstitial and bronchovascular inflammatory changes of sarcoidosis.[9] The most reliable test is a bronchoscopy, mediastinoscopy, or transbronchial procedure, to biopsy either lymph nodes or granulomas (see *Noncaseating granulomas in sarcoidosis*). The definitive test is a positive biopsy for sarcoidosis.[4] When

sarcoidosis presents with the sudden onset of weight loss and malaise, the expectation is a relatively short limited course. A chronic illness is suspected if onset is with dyspnea and skin involvement.

Gallium imaging can pinpoint areas of inflammation, although it is not specific for sarcoidosis.[4] Compromised pulmonary function indicates difficulties with expansion of the lungs or the exchange of oxygen and carbon dioxide. Another test is the Kveim-Siltzbach test, which is an injection of a standardized preparation of sarcoid tissue material into the skin that causes an elevated papule reaction, although a negative response does not eliminate sarcoidosis. This material is not easily available and is rarely used.[8]

Treatment and outcomes

The goals of treatment are to relieve symptoms, improve organ function, control inflammation, reduce the size of granulomas, and prevent pulmonary fibrosis. Treatment is based on symptoms, affected organs, and the level at which organs are functioning. The three stages of sarcoidosis are acute, chronic, and refractory. If there are no symptoms or significant changes in function, treatment is not indicated. Mild disease frequently resolves spontaneously without medication. However, if the eyes, heart, or brain are affected—even without symptoms—treatment is recommended.[7]



A chest X-ray can lead to early diagnosis by showing hilar lymphadenopathy, granulomas, or fibrosis.

Corticosteroids can decrease inflammation and formation of granulomas. The drug of preference is prednisone, with a typical dosage of 40 mg to 60 mg/day for 8 to 12 weeks followed by tapering down. Dosage may vary based on severity and response. Corticosteroids are powerful anti-inflammatory drugs that mimic the adrenal glands and should be used at the lowest effective dosage. Adverse affects include increased risk of infection, mood swings, weight gain secondary to fluid retention, elevated blood glucose, and increased appetite. Long-term use increases the risk of ulcers, acne, osteoporosis, hypertension, and cataracts.[7] For hypercalciuria, prednisone may be used and the patient should be advised to avoid calcium-rich foods, vitamin E, and sunlight.

If the acute process doesn't resolve and becomes a chronic illness, treatment may be more involved and longer. Refractory sarcoidosis does not respond to standard treatment. Immunosuppressant drugs and alternative therapy, such as melatonin, may also be used in refractory cases or nonresponsive cases. Two immunosuppressive drugs, methotrexate (Rheumatrex, Trexal), which is especially effective when lungs, eyes, skin, and joints are involved, and hydroxychloroquine (Plaquenil) for the nervous system, are helpful. These drugs suppress alveolitis and destroy the cells that produce granulomas; however, there are few clinical trials to support their use.

One trial of cyclosporine, used to suppress the immune system in organ transplant patients, was not successful in treating sarcoidosis. Thalidomide (Thalomid) limits alveolitis, increases lung function, and heals skin lesions. Infliximab (Remicade) has been reported effective.[14]

Melatonin regulates immune function and may inhibit the development of fibrosis. Melatonin was used in a trial with prednisone to treat sarcoidosis. Improvement was shown with melatonin, but it could have been placebo effect or delayed response to the prednisone.[15] Antitumor-necrosis factor-alpha etanercept (Enbrel), used for RA, was actually found to cause sarcoidosis.[1]

There is no current treatment to reverse fibrosis. Cardiac and lung transplantation may be an option for some patients who have refractory disease that no longer responds to medical therapy.[1]

Risks for poor outcomes include lung scarring, complications affecting the heart or brain, and lupus pernio on the skin. However, half of all cases do resolve within 12 to 36 months, and most within 5 years. Some may last longer, up to several decades. Sarcoidosis resolves without treatment in 60% to 70% of cases.

The NP's role

The NP integrates detailed history, physical exam, and diagnostic testing into determining the treatment plan. Complete medical history of the patient and family may provide significant clues. Patient anxiety may be increased by a lack of understanding the disease. Assessing educational needs and using appropriate materials will help the patient understand the disease process, treatment, and psychosocial concerns.

The decision to refer is based on the presentation and prognosis of the disease. The NP may remain involved and coordinate patient care. The interdisciplinary team will vary in relation to the affected system, such as a dermatologist, pulmonologist, ophthalmologist, neurologist, cardiologist, radiologist, or gastroenterologist. A team approach combines the expertise of a specialist and the holistic approach

of the NP. Tertiary care may provide more experience with this diagnosis and treatment. The focus of the multidisciplinary team is on physical, somatic, and psychosocial interventions and outcomes. The use of a multidisciplinary approach will enhance professional interest and knowledge of the disease.[16] Patients will need a strong support system and should consider a support group. All patients need periodic follow-up for assessment, eye exam, chest X-ray, and pulmonary function tests. For patients with cardiac involvement, follow-up testing includes electrocardiogram, echocardiography, and radionuclide imaging to evaluate disease progression.

Research regarding sarcoidosis is ongoing, leading to more accurate diagnosis and treatment. The link between sarcoidosis and cancer remains uncertain. Understanding how the interaction of the immune system, genetics, and environment cause the disease will improve treatment regimens and outcomes. NP

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