Sarcoidosis

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KEYWORDS

• Sarcoidosis • Management • Pulmonary • Extrapulmonary

Sarcoidosis is a multisystem granulomatous disorder of yet unknown etiology,[1] which predominantly involves the lungs in more than 90% of cases but can also involve any organ in the body, with the lymphatics, skin, eyes, and liver being the most common.[1,2] It was first described in 1877 by Jonathan Hutchinson when he described a patient with raised purple skin lesions, but it was Caesar Boeck who coined the term "sarkoid" when he described the histologic appearance of the skin lesions that he thought resembled sarcoma.[1]

EPIDEMIOLOGY

Sarcoidosis is a worldwide disease but with variable incidences, manifestations, and prognosis.[1] In the United States, the age-adjusted annual incidence rate in Caucasians is 10.9 in 100,000 and in African Americans it is 35.5 in 100,000.[1] In Spain the incidence rate is 1.3 in 100,000,[3] in Eastern Europe 3.7 in 100,000[3] and in Japan 1 in 100,000.[3,4] Sarcoidosis can affect any age group but tends to affect adults 40 years old or younger in the United States.[1] In Japan, it exhibits two peaks in the third and seventh decades of life.[1] Female predominance is common among all regions of the world.[1,4]

Disease manifestation also varies by ethnicity. The Japanese have higher rates of cardiac and ophthalmic involvement whereas Puerto Ricans have a high rate of developing lupus pernio.[1] Lofgren's syndrome is more frequently seen in patients from southern Europe,[3] whereas African Americans tend to have skin involvement other than erythema nodosum, eye, liver, bone marrow, and extrathoracic lymph node involvement.[2]

PATHOPHYSIOLOGY

Environment

The current hypothesis is that sarcoidosis develops when a genetically susceptible host is exposed to a yet unidentified antigen(s) in the environment.[1] Several

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environmental and infectious agents have been proposed but none have been proven yet. As part of the ACCESS study (A Case Controlled Etiologic Study of Sarcoidosis), which recruited 736 incident cases of sarcoidosis and 706 matched controls, participants completed extensive exposure questionnaires.[5] Five occupations and 5 exposures were more prevalent in the sarcoidosis group. Occupations included agricultural employment, physicians, jobs raising birds, jobs in automotive manufacturing, and middle/secondary school teachers. Exposures included exposure to insecticides and employment in pesticide-using industries, occupational exposure to mold and mildew, occupational exposure to musty odors, and use of home central air-conditioning.[6] A study from Switzerland found a higher frequency of sarcoidosis in regions with metal industry and intense agriculture.[7] In addition, in the aftermath of the 9/11 attacks, sarcoid-like granulomatous pulmonary diseases are being reported at higher rates than in the general population.[8,9] Infectious agents, particularly Mycobacteria, are reemerging as a potential antigen in sarcoidosis, with studies detecting Mycobacteria proteins in tissues from sarcoidosis patients and T cells from sarcoidosis patients responding to stimulation by Mycobacteria antigens.[10–17] Smoking appears to have a protective effect against sarcoidosis.[6,18,19] In the ACCESS study, sarcoidosis subjects were less likely to be smokers or ever-smokers than matched controls.[6] In addition, smoking sarcoidosis patients tended to have less thickening of their bronchovascular bundle on computed tomography (CT) scans.[19]

Chronic beryllium disease is a granulomatous disorder that affects predominantly the lungs, and can be mistaken for sarcoidosis if a history of beryllium exposure is not elicited.[20] Beryllium is a hard metal that is used in several industries including aerospace, automotive parts, computers and electronics, defense, dental, foundries, smelting, recycling, and telecommunications among others.[21] Exposure to beryllium can lead to beryllium sensitization, which can progress to chronic beryllium disease.[21] Beryllium sensitization has also been reported in household members of beryllium workers and from communities downwind from industries using beryllium.[21]

Genetics

The disparity in prevalence and variability of organ involvement between ethnic groups[1] and the familial clustering of sarcoidosis[22] strongly support a genetic basis for sarcoidosis. Several genome-wide association studies have identified potential association of specific genetic loci with sarcoidosis,[23–25] and several studies have also associated various human leukocyte antigen markers and gene-specific single nucleotide polymorphisms[26–28] with the risk, disease course, and organ involvement with sarcoidosis, indicating that sarcoidosis is a multigenetic disease.

Immune Response

Sarcoidosis is a T-helper 1 (Th1) cell biased disease.[1] Antigen presentation in the context of major histocompatibility complex II leads to activation of Th1 cells and subsequent production of various cytokines and chemokines including, but not limited to, interferon-γ, tumor necrosis factor (TNF)-α, transforming growth factor β, interleukin (IL)-2, IL-12, and others.[29] The immune response ultimately leads to the formation of granulomas, which consists of a central core of mononuclear cells surrounded by CD4+ cells and a small number of CD8+ and B cells.[29] A role for regulatory T cells has been proposed, but its exact role in sarcoidosis is yet unknown.[30] Sarcoidosis is also known for its immune paradox with an intense immune response in the organ involved and concomitant peripheral anergy.[29] The peripheral anergy manifests as lack of response to antigen skin testing and relative lymphopenia in the peripheral blood.[29] The exact cause of the peripheral anergy is yet unknown.[29]

Diagnostic Criteria

Sarcoidosis is characterized by the formation of well-formed, nonnecrotizing granulomas in affected organs (**Fig. 1**).[1] There are no formal diagnostic criteria for sarcoidosis, and the presence of noncaseating granulomas does not confirm the diagnosis of sarcoidosis on its own.[1] Sarcoidosis is a diagnosis of exclusion and as such, other causes of granulomas, infectious and noninfectious, need to be evaluated for and ruled out by obtaining a complete medical, occupational, environmental, and medication history as well as physical examination, followed by the appropriate diagnostic testing (**Table 1**).[31]

CLINICAL PRESENTATION

Sarcoidosis is a multisystem disease that can affect any organ.[1] The clinical presentation can vary from asymptomatic organ involvement that is detected incidentally to a slowly progressive disease. An acute form of sarcoidosis, Lofgren syndrome, is defined as an acute onset of fever, erythema nodosum, polyarthritis, and chest radiograph showing bilateral hilar lymphadenopathy with or without parenchymal infiltrates. Lofgren syndrome typically portends an excellent course, with spontaneous resolution.[1,32] The pulmonary system is involved in more than 90% of cases followed by skin, lymph nodes, eyes, and liver.[1,2] In the ACCESS study, half of the sarcoidosis cohort had only one organ involved, 30% had 2 organs involved, 13% had 3 organs involved, and 7% had 4 or more organs involved with sarcoidosis.[2]

Pulmonary

The lungs are the most common organs involved in sarcoidosis.[2] Presenting symptoms are variable. Patients can be asymptomatic with their disease identified on chest imaging obtained for unrelated reasons, but more commonly they have nonspecific symptoms such as cough, fatigue, and dyspnea on exertion. On physical examination, findings can include normal pulmonary examination, dry inspiratory crackles or wheezes from airway involvement with sarcoidosis, or airway distortion from fibrotic changes.[1] Pulmonary function testing can also be variable and may include normal, restrictive, or obstructive patterns with or without bronchodilatory responses, and a normal or reduced diffusion capacity.[33] The Scadding chest radiography staging system is the most common method used to describe chest radiographic findings in sarcoidosis patients, and depends on the presence and absence of hilar lymph

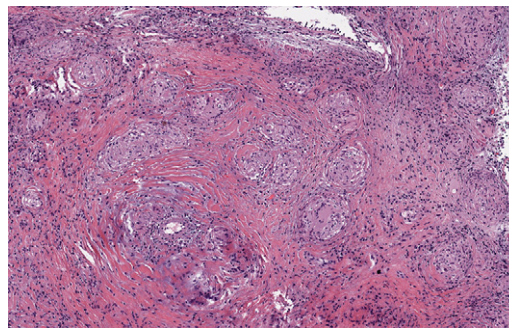

Fig. 1. Noncaseating granuloma. Multiple noncaseating granuloma from lung biopsy (hematoxylin-eosin stain, original magnification ×10). (*Courtesy of* Dr Steve Groshong, National Jewish Health.)

Table 1
Causes of granulomatous diseases

Causative Agent	Granulomatous Disease
Infectious	
Mycobacteria	Tuberculosis
	Atypical mycobacteria infection
Fungi	Histoplasmosis
	Coccidiomycosis
Bacteria	Brucellosis
	Chlamydia infections
	Tularemia
Parasites	Leishmaniasis
	Toxoplasmosis
Occupational and Environmental Exposures	
Organic agents	Hypersensitivity pneumonitis
Heavy metals	Chronic beryllium disease
	Other heavy metals (titanium, aluminum, zirconium)
Drug-induced	Methotrexate-induced pneumonitis
Neoplasia	Lymphoma
	Other tumors—sarcoidlike reactions
Autoimmune disorders	Wegner granulomatosis
	Primary biliary cirrhosis
	Churg-Strauss disease

Data from Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997;336(17):1224–34.

node enlargement and parenchymal infiltrates on chest radiograph (**Table 2**).[34,35] Chest CT findings include presence or absence of hilar and/or mediastinal lymphadenopathy with or without calcifications, nodular opacities in a perilymphatic distribution, parenchymal opacities, fibrosis with or without traction bronchiectasis, and airway narrowing due to intrinsic airway involvement or extrinsic compression by enlarged lymph nodes.[36] Pleural effusions are rarely seen in sarcoidosis.[37] Workup and follow-up for pulmonary sarcoidosis includes history to determine extent of and changes in dyspnea on exertion, chest radiography, pulmonary function testing, and walk oximetry to assess for oxygen desaturation.[1] Indications for immunosuppressive therapy for pulmonary sarcoidosis depend on the extent of symptoms and evidence of disease progression on follow-up.[1] Therapeutic regimens include corticosteroids and

Table 2
Scadding chest radiograph stages

Scadding Stage	Radiographic Description
0	Normal
I	Bilateral hilar lymphadenopathy *without* parenchymal changes
II	Bilateral hilar lymphadenopathy *with* parenchymal changes
III	Parenchymal changes *without* hilar lymphadenopathy
IV	Pulmonary fibrosis, conglomerate mass formation

steroid-sparing agents such as methotrexate, mycophenolate mofetil, azathioprine, leflunomide, and/or anti–TNF-α agents.[38–41]

Skin

Skin is the second most common organ involved in sarcoidosis, and is seen in 20% to 35% of sarcoidosis patients.[2,42–44] Manifestations of cutaneous sarcoidosis are variable and are categorized as specific and nonspecific lesions. Specific lesions include lupus pernio, maculopapular eruptions, subcutaneous nodules, plaques, and infiltrated scars, and typically show noncaseating granulomas when biopsied. Nonspecific lesions such as erythema nodosum are reactive in nature and do not demonstrate noncaseating granulomas when biopsied.[42–45] Cutaneous sarcoidosis has a predilection for scars and tattoos.[43] Management of cutaneous sarcoidosis is usually accomplished in collaboration with a dermatologist. Depending on the extent and severity of involvement, treatment options include topical steroids, local steroid injections, oral steroids, hydroxychloroquine, methotrexate, and anti–TNF-α agents in cases of recalcitrant lupus pernio.[43,44]

Eyes

Ocular involvement is variable across ethnic groups and can been seen in 10% to 80% of sarcoidosis patients.[1,46–50] Ocular involvement can be the initial manifestation of sarcoidosis.[48] All sarcoidosis patients require an annual ophthalmologic evaluation with a slit lamp, as most patients can be asymptomatic.[1] The most common manifestation is anterior uveitis, but any part of the orbit or adnexa can be involved.[46–50] It can present insidiously or acutely,[46–50] and can lead to visual impairment.[51] Management of ocular sarcoidosis is accomplished in collaboration with an ophthalmologist. Pharmacologic regimens include local topical or injectable steroids, and in refractory or recurrent cases second-line immunosuppressive agents such as methotrexate, leflunomide, mycophenolate mofetil, or anti-TNF agents have been used.[44] In addition to ophthalmic involvement with sarcoidosis, sarcoidosis patients need to be monitored for ophthalmic side effects and toxicities from immunosuppressive agents such as steroids and hydroxychloroquine that are used to manage other organ manifestations of sarcoidosis.[1]

Gastrointestinal

Sarcoidosis of the gastrointestinal system predominantly manifests as liver involvement.[52] The liver is involved in about 30% to 80% of sarcoidosis patients, whereas the gastrointestinal tract is rarely involved.[44,52,53] Hepatic sarcoidosis is twice as common in African Americans than in whites.[44,52] Patients can be asymptomatic or complain of nonspecific abdominal pain, pruritus, and/or jaundice.[44,52] Hepatomegaly is detected clinically in 21% of cases and radiographically in more than 50% of patients.[52] Pathological, findings include noncaseating granulomas mainly in the portal triad in addition to intrahepatic cholestasis and ductopenia with or without fibrosis.[44,52] Differential diagnosis for granulomas on liver biopsy should include primary biliary cirrhosis, tuberculosis, or drug reactions.[44,52,54] Hepatomegaly, lymphadenopathy, and low attenuating lesions of variable size in the liver can be seen on CT. On magnetic resonance imaging (MRI), nodules of various sizes with normal to slightly increased signal intensity can be seen.[44,52] Potential complications from hepatic sarcoidosis include cirrhosis and portal hypertension. Portal hypertension can be present with or without cirrhosis and can also develop from compression of the portal vein by enlarged lymph nodes in the hepatic hilum.[44,52] Most patients with hepatic sarcoidosis do not need therapy, especially if they are asymptomatic.[44,52] For

symptomatic patients, low-dose steroids (10–20 mg daily) is usually adequate to control symptoms,[44,52] although hepatic sarcoidosis can progress even with biochemical improvement,[53] and poor responses are usually seen in the setting of established cirrhosis and/or portal hypertension.[44,52] Other agents such as azathioprine, methotrexate, and anti–TNF-α agents have been used to manage hepatic sarcoidosis.[44,52] Ursodeoxycholic acid has been reported to improve symptoms associated with cholestasis in case reports and series.[55] Liver transplant is rarely needed for hepatic sarcoidosis but is successful, with survival rates comparable with those for other indications for liver transplant.[44,52]

Neurologic

Neurosarcoidosis affects 5% to 15% of sarcoidosis patients.[56,57] Any part of the nervous system can be affected but cranial nerves are those most affected, the facial nerve being the most common followed by the optic nerve.[56,57] Parenchymal brain lesions occur in 50% of cases, the meninges are involved in about 20% to 40% of neurosarcoidosis cases, and spinal involvement occurs in fewer than 10% of cases.[56,57]

About 10% of neurosarcoidosis cases are asymptomatic.[56] The signs and symptoms are nonspecific and include cranial neuropathies, meningeal irritation, increased intracranial pressure, peripheral neuropathies, endocrine dysfunction, cognitive dysfunction, and personality changes.[56,57] Fifty percent of patients present within 2 years of diagnosing sarcoidosis.[56]

Diagnosing neurosarcoidosis can be challenging, and other diagnoses with similar manifestations need to be excluded.[56,57] MRI is the imaging modality of choice, but CT can be used in patients who cannot undergo MRI scanning although it has decreased sensitivity compared with MRI.[56,57] Findings on brain MRI include leptomeningeal enhancement, parenchymal lesions, thickening and enhancement of cranial nerves, and hydrocephalus.[56,57] Cerebrospinal fluid (CSF) findings are nonspecific and include lymphocytic pleocytosis, elevated protein level, decreased glucose level, and high opening pressure.[56,57] Although CSF findings are nonspecific, they are important in excluding other causes of the neurologic signs and symptoms.[56,57] The CSF angiotensin-converting enzyme level is nonspecific.[56,57] Electromyography and nerve conduction studies are helpful in assessing peripheral neuropathies.[56]

Diagnosing neurosarcoidosis can pose a challenge. Proposed diagnostic criteria by Zajicek and colleagues[58] include probable neurosarcoidosis, which requires pathologic confirmation of systemic sarcoidosis, clinical presentation suggestive of neurosarcoidosis, and the exclusion of other causes of neurologic dysfunction. If a beneficial response to therapy over a 1-year period is observed in addition to the aforementioned criteria, neurosarcoidosis is characterized as definite. Possible neurosarcoidosis is characterized by a clinical presentation suggestive of neurosarcoidosis but, without pathologic confirmation of systemic sarcoidosis and exclusion of other causes of neurologic dysfunction cannot be confirmed. Small-fiber neuropathy is a newly described entity in sarcoidosis whereby the patient presents with peripheral pain and signs and symptoms of autonomic dysfunction.[56,57] The exact etiology of small-fiber neuropathy in sarcoidosis is yet unknown.

Neurosarcoidosis requires treatment with immunosuppressive therapy to prevent irreversible neurologic deficits.[56,57] Steroids and second-line immunosuppressive agents such as methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and anti–TNF-α agents have all been used with variable success rates.[56,57] The dose and duration of therapy depends on the severity of symptoms and response to therapy.[56,57] Coordinating care with a neurologist who has expertise in neurosarcoidosis is essential.

Hypercalcemia/Hypercalciuria

Hypercalcemia occurs in about 10% of sarcoidosis patients, and hypercalciuria (>300 mg/d) is more common, occurring 3 times more than hypercalcemia.[59] 1α-Hydroxylase, which converts 25-hydroxycholecalciferol to the active form 1,25-dihydroxycholecalciferol, is expressed in the macrophages present in the granulomas and contributes to the abnormal calcium homeostasis seen in sarcoidosis.[59,60] Hypercalcemia and hypercalciuria are usually asymptomatic but could be the initial manifestation of sarcoidosis, with patients presenting with symptoms of hypercalcemia including lethargy, constipation, mental status changes, renal dysfunction, and/or nephrolithiasis. Management of hypercalcemia and/or hypercalciuria includes dietary modifications by avoiding dairy products and other nutrients high in vitamin D and calcium, and avoidance of sun exposure by wearing long sleeves and using sun-blocking products.[61] Other causes of hypercalcemia such as hyperparathyroidism should also be ruled out. Corticosteroids and hydroxychloroquine are the first line of therapy if hypercalcemia and/or hypercalciuria persist in spite of compliance with the aforementioned restrictions.[61]

Cardiac

Cardiac sarcoidosis is detected clinically in about 5% of cases, but on autopsy in about 40% of cases.[62,63] It can be asymptomatic or present with palpitations, dyspnea on exertion out of proportion to pulmonary involvement, syncope or presyncopal episodes or, rarely, sudden cardiac death.[62,63] No official guidelines exist for screening and management of cardiac sarcoidosis.[64] Screening for cardiac sarcoidosis is by history, physical examination, and 12-lead electrocardiogram (ECG).[1] Transthoracic echocardiogram and ambulatory ECG (Holter and event monitors) are helpful in further investigating symptoms that are suspicious of potential cardiac sarcoidosis.[1,63] Cardiac MRI (cMRI) and cardiac ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET) imaging are new modalities used in the assessment of cardiac sarcoidosis.[65–67] Abnormalities on 12-lead ECG and ambulatory ECG include high-grade conduction blocks and ventricular and atrial arrhythmias.[63] Abnormalities on echocardiogram include unexplained left ventricular dysfunction and wall motion abnormalities.[63] cMRI findings suggestive of cardiac sarcoidosis include delayed hyperenhancement in a noncoronary distribution, suggestive of scar formation, in addition to wall edema.[63] Abnormalities on cardiac FDG-PET include hypermetabolic activity in a patchy or patchy-on-diffuse pattern.[63] Management of cardiac sarcoidosis includes immunosuppressive therapy, arrhythmia management, and management of any underlying left ventricular dysfunction.[68] Electrophysiological studies are important in risk assessment for sudden cardiac death and in determining when an automated implantable cardiac defibrillator is indicated.[69]

Musculoskeletal

Sarcoidosis can involve the articular, skeletal, and muscular systems.[70] Acute arthritis is reactive in nature and commonly manifests as part of Lofgren's syndrome.[70] Chronic arthritis is uncommon (1%–4% of cases), is associated with noncaseating granulomas and lymphocytic infiltration of involved joints, and usually denotes a chronic course.[70] Bone involvement is usually asymptomatic and is detected incidentally. It usually affects the small bones of the hands and feet but can affect any bone.[70] Radiographic findings include osteolysis in the small bones of the hands and feet and osteosclerosis in the long bones and vertebrae.[70] Bone scans and PET can also detect increased activity in the involved bones.[70] Muscle involvement

is rare and can present as chronic myopathy, nodules, or masses, and rarely as acute myositis.[70] Management is mainly symptomatic, and includes steroids with or without second-line immunosuppressive agents.[70]

SYNDROMES OF SARCOIDOSIS

Lofgren's syndrome was first described in 1952.[71] Lofgren's syndrome is the acute manifestation of sarcoidosis, typically presenting in the springtime with arthritis, erythema nodosum, uveitis, and enlarged hilar lymph nodes.[72] It usually has an excellent prognosis, with high rates of spontaneous remission.[1] In the United States about 10% of the patients present with manifestations of Lofgren's syndrome, whereas it is rare in Japan but very common in Spain, where about half of the patients present with the syndrome, mostly in the spring.[3] Lofgren's syndrome typically has a benign, self-resolving course. Therapy is usually aimed at symptomatic relief, and includes short courses of nonsteroidal anti-inflammatory agents or corticosteroids.[72]

Heerfordt syndrome, also known as uveoparotid fever, was first described in 1909.[73] Patients present with fever, parotid gland enlargement, anterior uveitis, and facial nerve palsy.[73]

SUMMARY

Sarcoidosis is a multisystem disease with variable presentations, organ manifestations, and disease courses.[1] Histologic confirmation is necessary to confirm sarcoidosis but can be waived in cases of typical Lofgren's syndrome. In assessing a newly diagnosed patient a thorough history, including environmental and occupational history, and physical examination are essential in assessing organ involvement and for exclusion of other disorders that can be mimicked by sarcoidosis.[1] Laboratory and radiographic investigations include chest radiography, pulmonary function testing, annual ophthalmologic examination, 12-lead ECG, comprehensive metabolic panel, and 24-hour urinary calcium level.[1] Other investigations to assess organ involvement are typically guided by the findings of history and physical examination.[1] Sarcoidosis patients need routine follow-up to assess potential organ involvement, disease progression, and response to therapy when instituted.

Management of sarcoidosis patients is best accomplished in collaboration with a sarcoidosis center or expert, and appropriate subspecialists as dictated by organ involvement. Immunosuppressive therapy is indicated when major organs are involved (neurologic, ophthalmologic, or cardiac) or when there is evidence of organ dysfunction or progressive disease in other organs.[1] Immunosuppressive regimens, when indicated, include corticosteroids and steroid-sparing agents, and close monitoring of potential side effects and toxicities of immunosuppressive regimens is necessary.[38,39]

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