Sarcoidosis

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KEYWORDS

• Sarcoidosis • Cutaneous sarcoidosis • Erythema nodosum • Lupus pernio
• Extracutaneous sarcoidosis • Granuloma • Therapy

KEY POINTS

- Sarcoidosis is a multisystemic granulomatous disease of unknown cause that affects the skin in 20% to 30% of cases.
- Sarcoidosis skin lesions may be specific, which tend to be chronic, or nonspecific, which tend to be acute.
- Lupus pernio is associated with chronic disease, whereas erythema nodosum is associated with acute disease and spontaneous resolution.
- Systemic treatment of the skin is reserved for symptomatic, widespread, disfiguring, and/or quality of life–altering disease and includes oral corticosteroids, methotrexate, antimalarials, minocycline, and some tumor necrosis factor inhibitors.
- The diagnosis of sarcoidosis requires a multimodal approach that comprises clinical findings, histologic presence of noncaseating granulomas, demonstration of organ involvement radiologically or through other tests, and exclusion of other diseases.

INTRODUCTION

Sarcoidosis is a chronic but frequently self-resolving disease of unknown cause characterized histologically by the formation of noncaseating epithelioid cell granulomas in one or more organs. The protean skin manifestations can confound even experienced dermatologists, and, in some cases, effective treatment is challenging. A reasonable diagnosis can be made in most cases from the appearance of skin lesions, confirmatory histology, involvement of other organ systems, and exclusion of other noncaseating granulomatous diseases. It must always be remembered that sarcoidosis is a potentially lethal and disabling disease with a broad spectrum of heterogeneous anatomic involvement leading to a remarkable range of possible symptoms that can mimic those of many other diseases. Therefore, sarcoidosis should be included in many clinical differential diagnoses (see **Table 2**). Evaluation of extracutaneous involvement should be performed at the initial presentation of sarcoidosis on any organ (**Box 1**),[1] and a review of systems should be part of follow-up visits. Collaborative communication between specialists and primary care physicians engenders better patient care.

Depending on study design and selected population, cutaneous disease has been reported to occur in 9% to 37% of all cases,[2,3] but in the ACCESS (A Case-control Etiologic Study of Sarcoidosis) study, specific lesions were present in 16%, similarly to the 17% reported in a recent study from Barcelona, Spain.[4] Cutaneous sarcoidosis is the initial manifestation of the disease in nearly one-third of patients.[5] The skin (as well as the liver, spleen, and lymph nodes) is most often involved in African Americans.

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Box 1
Recommended initial assessment for systemic disease in patients with suspected or diagnosed sarcoidosis

1. Comprehensive history: occupational and environmental exposures, detailed review of systems
2. Physical examination
3. Chest (posteroanterior, lateral) radiograph
4. Serum chemistries (including calcium, hepatic panel, and renal function tests to evaluate liver and renal function)
5. Complete blood count (including white blood cell count, hemoglobin, and platelet count)
6. Urinalysis
7. Twenty-four-hour urine collection for calcium
8. 25-Hydroxy vitamin D level
9. Pulmonary function test (spirometry, diffusion capacity, and total lung capacity)
10. Ophthalmologic examination: slit-lamp and fundoscopic eye examination
11. Electrocardiogram and echocardiogram: if abnormal, consider gadolinium delayed-enhancement cardiovascular magnetic resonance or fluorodeoxyglucose PET
12. Tuberculin skin test or interferon release assay to exclude tuberculosis and as a precaution in case immunosuppressive treatment needs to be initiated.

Abbreviation: PET, positron emission tomography.

Adapted from Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 1999;16(2):149–73.

EPIDEMIOLOGY

Sarcoidosis has been reported from practically all countries and in every race, but its prevalence varies by geographic location, ethnicity, gender, and age. In the United States, the lifetime risk for developing sarcoidosis was estimated to be 2.4% in African Americans and 0.84% in white people and the adjusted annual incidence is more than 3 times higher in the former (35.5 per 100,000) than the latter (10.9 per 100,000).[6,7] Women develop sarcoidosis more often than men,[8,9] but in both genders the incidence peaks between the ages of 25 and 45 years.[10] In Scandinavia, where the annual incidence is the highest in the world (64 cases per 100,000 people), incidence rates in women are bimodal with peaks occurring at 25 to 29 and 65 to 69 years of age.[1,8,11] In Japan, where the annual incidence is only 1 to 2 cases per 100,000 people, incidence rates peak between the ages of 20 and 34 years but a second peak occurs in women aged 50 to 60 years.[12] In a recent study, 35% of cases had skin involvement.[12] Alarmingly, the age-adjusted, sarcoidosis-related mortality in the United States increased 50.5% in women and 30.1% in men from 1988 to 2007.[13] The prognosis is especially grave in black women in whom sarcoidosis-related complications are the cause of death in 25% of those with the disease.[14]

ETIOPATHOGENESIS

Despite considerable effort, the cause of sarcoidosis has eluded investigators. The disease has been described as an immune paradox because peripheral anergy is present despite a brisk tissue inflammatory response.[15] Studies suggest that development of sarcoidosis involves an interplay between extrinsic antigens, genetic factors, and immune responses.[16,17] The regulation of immune mechanisms is more complex and extensive than can be discussed in this article,[18] but researchers have suggested that poorly degraded antigen is engulfed by antigen-presenting cells (APCs) and displayed on the APCs' major histocompatibility complex (MHC).[10,18] A CD4+ T-cell receptor attaches to this antigen-MHC complex and becomes activated. The result is a release of cytokines, including interleukin (IL)-2, which induce clonal proliferation of activated, strongly Th1 polarized T-helper cells that secrete proinflammatory cytokines, such as IL-2, IL-12, and IL-18 (interferon-gamma–inducing factor), which facilitate granuloma formation. Some selectins, integrins, cytokines (such as CXCL-8), and cellular adhesion molecules promote diapedesis of monocytes from blood vessels to activated tissue macrophages. Further release of cytokines and chemokines causes macrophage aggregation into granulomas.[10,18] Granulomas are composed of epithelioid cells, mononuclear cells, and CD4+ T cells with a few CD8+ T cells around the periphery. Recently, serum amyloid A was found to be present in granulomas and to amplify Th1 responses by interacting with Toll-like receptor 2. If Th1 immune responses predominate, upregulation of interferon-gamma, IL-10, and other cytokines results in antigen clearance and granuloma resolution. In more than 60% of sarcoidosis cases, the granulomas resolve within 2 to 5 years.[19] If Th-2 immune responses predominate, upregulation of