# Sarcoidosis

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Sarcoidosis is a systemic noncaseating granulomatous disorder of unknown origin. The cutaneous manifestations of sarcoidosis often enable the dermatologist to be the first physician to make the diagnosis. This article reviews essential sarcoidosis pathophysiology, clinical polymorphisms, systemic evaluation, and treatment modalities for cutaneous sarcoidosis to further enhance the dermatologist's understanding of this disease entity. (J Am Acad Dermatol 2001;44:725-43.)

***Learning objective:*** At the conclusion of this learning activity, participants should be familiar with the theories of the pathogenesis of sarcoidosis, its cutaneous manifestations, its various syndromes and associations, and its presentation in children. Participants should also be more knowledgeable about diagnostic evaluation, measurement of disease progression, treatment modalities, and the prognosis and mortality data of sarcoidosis.

## DEFINITION

In Greek, sarcoidosis means a fleshlike condition (*sarco* means "flesh," *eidos* means "like," and *osis* means "condition.")[1] In contemporary times, sarcoidosis is a multisystem disorder of unknown origin, characterized by the accumulation of lymphocytes and mononuclear phagocytes that induce the formation of noncaseating epithelioid granulomas with secondary derangement of normal tissue or organ anatomy and function. Evidence of sarcoidosis lasting longer than 2 years designates it as chronic.[2,3]

## EPIDEMIOLOGY

Sarcoidosis affects all races, both sexes, and all ages. Most commonly it presents in winter and early spring.[4] It usually peaks between the ages of 25 and 35 years; a second peak occurs in women aged 45 to 65 years.[1,5] Cases affecting African Americans have a tendency to be more acute and severe than in other races, whereas cases affecting white persons have a tendency to be asymptomatic with a more favorable prognosis.[6]

The worldwide incidence of sarcoidosis is reported as follows: Sweden, 64/100,000; United Kingdom, 20/100,000; France, 10/100,000; Germany, 9/100,000; Greece, 7/100,000; Spain, 1.4/100,000; Japan, 1.4/100,000.[7-9] In the United States the racial variation is 10/ to 14/100,000 for white persons and 35.5/ to 64/100,000 for African Americans.[10] Rybicki et al[11] found that the incidence of sarcoidosis in the Detroit metropolitan area was as follows: African American female patients, 39/100,000; African American male patients, 30/100,000; white female patients, 12/100,000; white male patients, 9/100,000. African American women between the ages of 30 and 39 years were found to have the highest annual incidence: 107/100,000.

*Abbreviations used:*

| | |
|---|---|
| ACE: | angiotensin-converting enzyme |
| EN: | erythema nodosum |
| IL: | interleukin |
| PCR: | polymerase chain reaction |
| TNF: | tumor necrosis factor |

## ETIOLOGY

The origin of sarcoidosis remains unknown.[12,13] Many postulations abound as to whether the cause is multifactorial or due to a single antigen-driven disease that has not yet been determined. The cause has been thought to be elusive because sarcoidosis is a disease with the following characteristic flaws: polymorphic disease presentations, overlap with other diseases, paucity of systematic epidemiologic investigations of cause, diagnostic access bias, misclassification of the disease because of insensitive

From the Department of Dermatology, University of Virginia.
No funds were received for the preparation of this article and none of the authors have any competing interests to disclose.
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0190-9622/2001/$35.00 + 0 **16/2/114596**
doi:10.1067/mjd.2001.114596

and nondiagnostic testing, and its diagnosis is one of exclusion.[13-15]

**Immunologic pathogenesis**

The development of noncaseating granulomas is thought to be the result of the local presentation of an antigen by macrophages to T lymphocytes, CD4 T cells/helper T cell type 1 ($T_H1$) phenotype.[16,17] The T cells most likely act in a twofold manner: in antigen recognition and in amplification of the local cellular immune response.[16] The CD4 T cells in sarcoidosis express α/β T-cell receptors and recognize antigens that are major histocompatibility complex (HLA) class II restricted (exogenous antigen presentation).[13,18] T-cell activation is also dependent on the interaction of the B7:CD28/CTLA-4 costimulatory pathway.[19]

A cellular redistribution from the peripheral blood and in situ proliferation account for the increased number of cells in tissues involved in the inflammatory process.[20] There is CD4 T-cell compartmentalization, when lymphocytes recognize specific adhesion molecules (ie, E-selectin) on endothelial cells.[21] Once compartmentalized the production of CD4 T-cell cytokines (interleukin 2 [IL-2], interferon gamma, IL-8, and tumor necrosis factor–α [TNF-α]), with other immune effector cells (macrophages, natural killer cells, and mast cells), enhance lymphocyte proliferation to induce granuloma formation.[22] Thus a highly focused, antigen-driven, overexuberant cellular immune response occurs within the target organ.[23] Vaalamo et al[24] found that macrophage production of metalloelastase contributes to elastin degradation and aids in the macrophage migration occurring in granulomatous diseases. The granulomas become hyalinized, then fibrotic, resulting in tissue scarring. This is believed to be a shift in cytokine profiles to that of $T_H2$ CD4 T cells (ie, IL-4), thereby causing a fibroproliferative phase.[22] The recruitment of CD4 T cells from the peripheral blood causes the development of anergy.[25] There is also resultant hypergammaglobulinemia from a nonspecific induction of polyclonal B-cell immunoglobulin production activated by the response of localized T cells.[9]

**Genetic pathogenesis**

A genetic origin is supported by the presence of positive familial clusters of sarcoidosis.[26] In the United States familial clusters occur more commonly among African Americans.[27] Genetic variations that promote susceptibility to the disease could reside in loci that influence immune regulation, T-cell function, or antigen presentation. Primary associations through serologic studies have shown patients with certain class I and II HLA alleles, found on chromosome 6, may have increased susceptibility to sarcoidosis.[28]

Martinetti et al[29] found that the heterogeneity of HLA polymorphisms mirrors the heterogeneity of the disease. Of 233 European patients with sarcoidosis, there was a positive association with HLA-1, -B8, and -DR3. There was also a positive association with HLA-B27 and disease limited to the lungs. There was a negative association with HLA-B12 and -DR4. HLA-B13 and -B35 were associated with early onset of disease, and HLA-DR3 was found to be associated with good outcome. Ishihara et al,[30] with the use of polymerase chain reaction (PCR)–restriction fragment polymorphism, pinpointed the HLA-DRB1 locus to determine susceptibility to sarcoidosis. Further genetic studies have found that angiotensin-converting enzyme (ACE) gene polymorphism might play a role in sarcoidosis,[31] that polymorphic variation of the *TAP2* gene does not confer susceptibility,[32] and that the presence of GLU residue at position 69 of HLA-DPB1 may play a role in sarcoidosis.[33] The expression of the acute phase reactant genes *ORM1* (of orosomucoid) and (*HP1*) of haptoglobin are also increased in sarcoidosis.[34]

**Infectious pathogenesis**

Definitive identification and proof of an infectious agent are still lacking. Cases in which sarcoidosis developed after transplantation of organs from a person with sarcoidosis suggest that a causative agent may be infectious.[35] In contrast, Fite et al[36] found that chest radiography performed on 239 familial contacts of German patients with sarcoidosis showed no evidence for communicable spread of the disease.

The association of tuberculosis and sarcoidosis remains controversial (TB or not TB). Because of the use of PCR, *Mycobacterium* has re-emerged as a possible transmittable agent in sarcoidosis. Popper et al[37] found that 11 of 35 cases of sarcoidosis lung tissue had mycobacterial DNA sequences. Kon and du Bois[38] found that acid-fast cell wall–deficient forms of bacteria grew from the blood of 19 of 20 patients with sarcoidosis. Monoclonal antibody staining and modified Kinyoun stain confirmed a mycobacterial origin. el-Zaatari et al[39] isolated and identified cell wall–deficient forms of bacteria with PCR amplification from sarcoidosis-affected skin, cerebral spinal fluid, and culture isolates. They demonstrated *M paratuberculosis* or a closely related *M avium*, but no *M tuberculosis*. Vokurka et al,[40] using PCR, found no detectable *M tuberculosis* in 15 cases of lung and lymph node sarcoidosis. Richter et al,[41] by coding for 16S ribosomal RNA which is present in all mycobacterial species, found 23 lung tissue

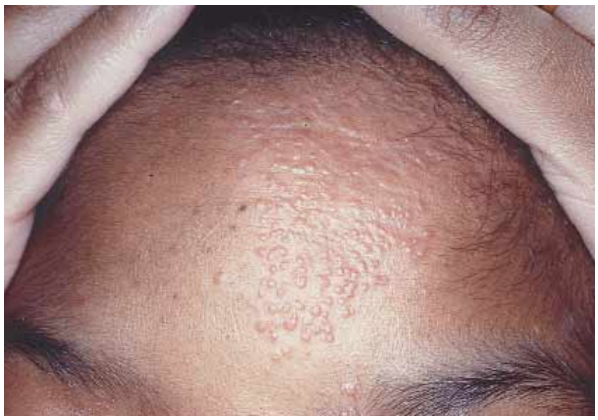

**Fig 1.** Maculopapular sarcoidosis.

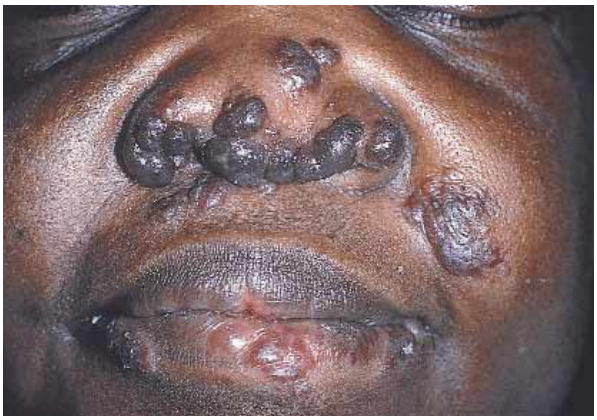

**Fig 2.** Nodular sarcoidosis.

samples from patients with sarcoidosis that were negative for mycobacterial DNA.

Therefore PCR studies for the detection of mycobacterial DNA have been shown to be inconclusive. PCR is not a good tool in the quest for the pathogenesis of sarcoidosis because it does not discriminate between living or dead mycobacteria, and it is fragile and easily contaminated.[42,43] Additional evidence against the role of mycobacteria in sarcoidosis includes lack of cultured mycobacteria from sarcoidosis tissues, the fact that fulminant mycobacterial disease does not develop with the use of immunosuppressive agents in patients with sarcoidosis, the fact that BCG vaccination has not been shown to reduce the incidence of sarcoidosis, and the fact that antituberculosis medications are ineffective.[43-45]

Di Alberti et al[46] suggested a viral origin of sarcoidosis, when they demonstrated a high detection rate of human herpesvirus-8 ORF 26 DNA in sarcoidosis tissue. Granieri et al[47] found only 8 patients with both sarcoidosis and HIV described up to 1995. Mirmirani et al[48] reported the development of sarcoidosis after immune restoration in HIV-positive patients treated with antiretroviral therapy. A multicenter study supported by the National Institutes of Health, named ACCESS (A Case-Controlled Etiologic Study of Sarcoidosis), is currently under way.[15] The study includes family studies, DNA analysis, and a careful search for possible infectious agents as the cause for sarcoidosis.

### Environmental pathogenesis

Some inorganic antigens suggested in the origin of sarcoidosis have included clay, talc, pine pollen, oxalosis, and beryllium.[38] Occupational environmental associations have been health care workers,[49] firemen,[50] and navy personnel on aircraft carriers.[51] Sarcoidosis is found to be more common in nonsmokers than in smokers.[52] Wilsher[53] found seasonal clustering of sarcoidosis presenting with erythema nodosum to occur in the spring months. This suggests an environmental trigger in the origin of sarcoidosis.

## CUTANEOUS MANIFESTATIONS

On average, 25% of sarcoidosis cases have cutaneous involvement that can occur at any stage; however, most often cutaneous involvement occurs at onset of the disease.[13,54,55] In general specific skin lesions have no prognostic significance, do not show any correlation with the extent of systemic involvement, and do not indicate a more serious form of sarcoidosis.[55-57] This is with the exception of erythema nodosum (EN), which has been shown to have a good prognosis because of its association with sarcoidosis that resolves spontaneously.[58-60] However, Olive and Kataria[61] did note in a chart review of 329 patients with sarcoidosis that sarcoidosis skin lesions other than EN were more likely to have lymphadenopathy and hepatosplenomegaly than in sarcoidosis patients without skin disease. The dermatologist will often be the first to consider a diagnosis of sarcoidosis because of the cutaneous manifestations of the disease. Any granulomatous skin lesion without apparent diagnosis, screening for systemic sarcoidosis is indicated.[55,56] Sarcoidosis cutaneous lesions, especially those that are chronic, tend to be asymptomatic.[62]

Sarcoidosis lesions are classified as specific and nonspecific; specific lesions contain granulomas, and nonspecific lesions are reactive processes.[63] Common specific sarcoidosis skin lesions manifest as maculopapules, nodules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio.[54,56,64,65] Maculopapular lesions are the most common cutaneous manifestation of granulomatous involvement in sarcoidosis (Fig 1).[56,64,66] They are usually red-brown to purple


**Fig 3.** Subcutaneous sarcoidosis. (From Callen JP, Greer KE, Paller AS, Swinyer LJ. Color atlas of dermatology. 2nd ed. Philadelphia: Saunders; 2000. p. 107.)

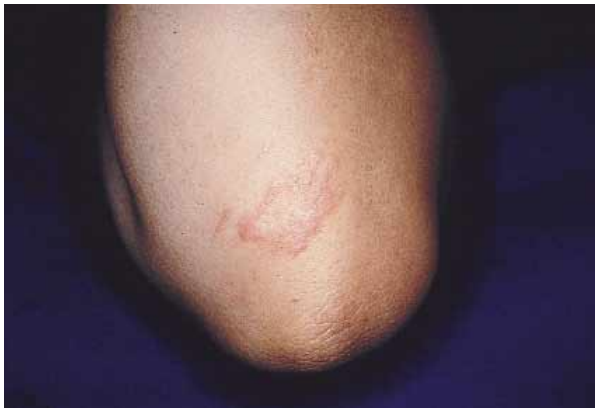

**Fig 4.** New-onset redness and fullness to a previously quiescent traumatic scar. Infiltrating scar sarcoidosis.

papules and measure less than 1 cm.[56] They are commonly found on the face, lips, nape of the neck, upper back, extremities, and rarely in the oral cavity (which often get confused with Fordyce spots).[54,56,64,67] They may be associated with acute forms of sarcoidosis with simultaneous parotid, ocular, lymph node, or pulmonary involvement.[56,57] Diascopy of the lesions gives the appearance of an "apple-jelly" color, but this change is not specific to sarcoidosis.[68] Nodular lesions occur more frequently on the torso or extremities, but may occur on the face (Fig 2).[65]

Skin plaques are round to oval red-brown lesions, which are generally elevated with induration, and occur on the face, scalp, back, shoulders, arms, and buttocks.[56,64] Annular plaques can occur on the forehead and lead to scarring and alopecia.[69] Skin plaques of the head and neck are seen in association with chronic sarcoidosis.[56,70]

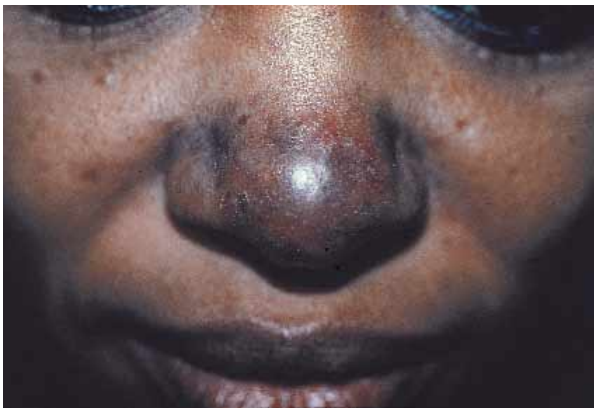

**Fig 5.** Lupus pernio. (Courtesy of military dermatology teaching files at Brooke Army Medical Center, Ft Sam Houston, Tex.)

Subcutaneous nodules are painless, firm, mobile nodules measuring from 0.5 to 2 cm without epidermal involvement (Fig 3).[56,64,70] The number of nodules can range from 1 to 100 and most frequently the nodules appear late in the course of the disease.[56,70] They can be associated with lung, liver, and spleen sarcoidosis.[70]

Inactive scars that have been quiescent for years that become infiltrated with sarcoidosis develop a red or purple hue with induration (Fig 4).[56,64,71] They may appear early in the disease before the onset of pulmonary disease or parallel chronic systemic findings.[56,72] Patients with sarcoidosis in remission in whom changing scars develop show possible reactivation of their sarcoidosis.[71] The pathogenesis of infiltrative scar sarcoidosis is unknown.[71]

Lupus pernio is the most characteristic skin lesion of sarcoidosis.[54,56] It is most common in African American women and is the hallmark of fibrotic disease.[62,73] It consists of indolent, indurated, red-brown to purple, swollen, shiny skin changes on the nose, lips, cheeks, and ears (Fig 5).[54,62,64] Lesions of lupus pernio can be disfiguring.[12] Lupus pernio coexists with chronic fibrotic sarcoidosis of the upper respiratory tract, with nasal, pharyngeal, and laryngeal involvement, pulmonary fibrosis, chronic uveitis, and bone cysts.[56,57,62,73]

Multiple manifestations in the skin with underlying granulomatous changes (specific) have been reported, to some extent mimicking syphilis with its protean manifestations (Fig 6). Acquired ichthyosis is a specific sarcoid cutaneous finding but not a common presentation (Fig 7).[65,74] The differential diagnosis includes sarcoidosis, lymphoma, solid malignancies, HIV and mycobacterial infection, medication-induced connective tissue disease, malnutrition, and parathyroid/thyroid disease.[74]

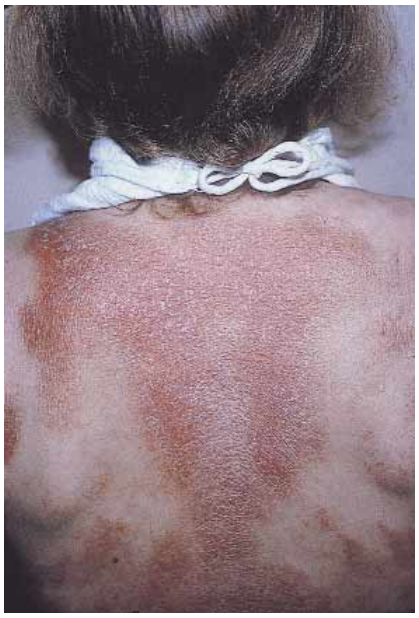

**Fig 6.** Atypical erythematous exfoliative sarcoidosis.

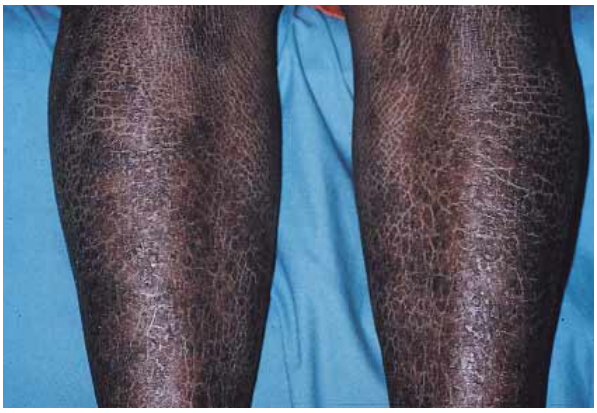

**Fig 7.** Sarcoidosis ichthyosis.

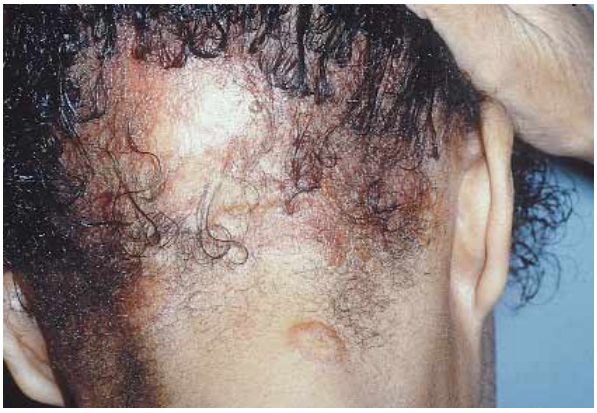

**Fig 8.** Scarring alopecia due to sarcoidosis.

Some documented uncommon atypical specific presentations of sarcoidosis are ulcerative,[75] psoriasiform,[75] hypopigmented,[76,77] faint erythema,[78] verrucous,[75] ichthyosiform,[74,79] folliculitis,[80] lichenoid,[81] eruptive,[81] erythrodermic,[79,80] cicatricial alopecia (Fig 8),[69] mutilating lesions,[75,82] erythematous plaques of palms and soles,[80] unilateral lower extremity edema,[83] nodular finger tip lesions,[84] penile (Fig 9),[85] granulomatous cheilitis,[67] scalp nodules,[86] erythema annular centrifugum,[87] annular elastolytic,[88] palmar erythema,[89] rosacea-like syndrome,[90] vulvar,[91] morpheaform,[63] light-exposed papules,[64] angiolupoid,[92] perforating,[93] lupus erythematosus–like,[12] and umbilicated.[66]

A nonspecific lesion that is considered the hallmark of acute and benign sarcoidosis is EN (Fig 10).[56,59] When associated with bilateral hilar adenopathy with or without pulmonary fibrosis, migratory polyarthritis, fever, and iritis, it is called Löfgren's syndrome.[94,95] Neville, Walker, and James[60] studied 251 cases of sarcoidosis presenting with EN; 83% of patients had remission of their sarcoidosis in 2 years, whereas 16% had active disease 2 years after presenting with EN. Mana, Salazar, and Manresa[58] noted in a multivariate analysis of 209 patients over a 14-year period that the absence of EN was a risk for persistent disease activity in sarcoidosis. Other nonspecific changes seen with sarcoidosis are calcifications, prurigo, and erythema multiforme.[64]

Nonspecific and specific nail changes that occur with sarcoidosis include clubbing,[64] dystrophy with and without underlying bone cysts,[96,97] subungual hyperkeratosis,[96,98] and onycholysis (Fig 11).[99]

## CLINICAL POLYMORPHISMS OF SYSTEMIC SARCOIDOSIS

In patients with sarcoidosis, one third can present with nonspecific constitutional complaints including fever, fatigue, malaise, and weight loss.[62] Post-sarcoidosis chronic fatigue syndrome may be difficult to separate from low-grade persistent sarcoidosis.[100] Sarcoidosis is also in the differential diagnosis of a fever of unknown origin.[62] Other symptoms can be associated with the specific organ system affected. Johns and Michelle[15] noted that extrathoracic manifestations of sarcoidosis are more common in African American patients.

Lung manifestations occur in nearly all cases (90%) of sarcoid.[62] Lung disease is mainly granulomatous involvement of interstitial areas, affecting alveoli, blood vessels, and bronchioles.[101] These pulmonary changes lead to dry rales, restricted lung volumes,

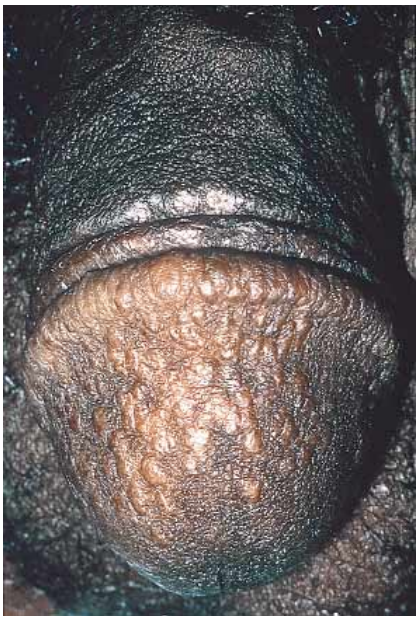

**Fig 9.** Penile sarcoidosis.

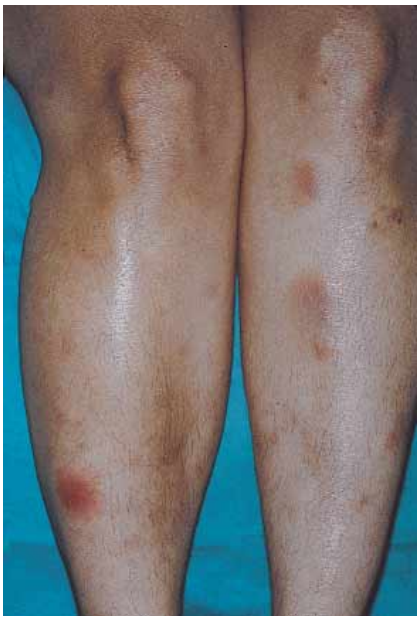

**Fig 10.** Erythema nodosum. A reactive form of sarcoidosis.

and abnormal gas exchange.[101] In 10% to 15% of patients there is irreversible fibrosis and severe disability.[9] Pleural effusions with infiltration of pleura are documented, but rare.[102] Symptoms of lung disease include dyspnea, cough, chest pain, and rarely hemoptysis.[103] Radiographically, sarcoidosis of the lung is staged.[15] Stage 0 is normal; stage I is bilateral hilar and/or para tracheal adenopathy; stage II is adenopathy with pulmonary infiltrate (Fig 12); stage III is pulmonary infiltrates only; stage IV is pulmonary fibrosis. The stages are not chronologic in nature.[44]

Intrathoracic and peripheral lymphatic adenopathy is common in sarcoidosis. Up to 90% of patients present with hilar or paratracheal (or both) adenopathy.[9,13] Peripheral nodes are usually asymptomatic and nontender (Fig 13). Bone marrow and hematologic changes of sarcoidosis are seen in up to 40% of cases, manifesting as leukopenia, lymphocytopenia, and an elevated erythrocyte sedimentation rate.[104]

The liver and spleen are involved between 50% and 80% of the time.[13,62,105] Hepatic granulomas are usually asymptomatic, but may cause obstructive jaundice.[106] Liver function tests such as alkaline phosphatase may be abnormally elevated with hepatic involvement.[9] Splenomegaly from granulomatous sarcoid infiltration is associated with a poor outcome because of its association with extensive fibrotic changes in other organs.[107]

Musculoskeletal involvement has been reported to occur in up to 39% of patients with sarcoidosis.[108] Clinically muscular involvement may be evident because of weakness, pain, tenderness, and erythema with warmth of the overlying skin.[15] Musculoskeletal manifestations include bone cysts and osteolytic lesions,[109] chronic myopathy,[110] muscle nodules,[111] tumorlike lesions,[112] arthralgias, arthritis, and tenosynovitis.[113,114]

Ocular manifestations are present in 30% to 50% of cases.[115] There is a definite threat of blindness, and all patients need eye examinations, even if they have no symptoms.[115] Sarcoidosis classically presents as acute anterior uveitis.[116] There may also be blurred vision, photophobia, and excessive lacrimation. Other ocular lesions include posterior uveitis, conjunctival nodules, scleral plaques, lacrimal gland enlargement (Fig 14), and iritis.[116]

Involvement of the upper respiratory tract is found in 5% to 20% of cases[117] and can present as lupus pernio. There can be granulomatous invasion of nasal and oral mucosa,[118] larynx and pharynx,[119] salivary glands (sarcoidal ranula),[120] tonsil and tongue.[121] Enlargement of the parotid gland is found in 6% of patients.[122] Upper respiratory tract manifestations can lead to nasal congestion, palatal obstruction, and disfigurement.[123]

Cardiac manifestations occur clinically in 5% of cases and may cause serious sequelae.[124] In comparison at autopsy, 10% to 20% in the United States and 67% in Japan were found to have cardiac muscle granulomatous infiltration.[125] Sudden cardiac death can be the initial manifestation of cardiac sarcoidosis in 5% to 10% of cases.[13] Electrocardiographic abnormalities such as complete heart block and other arrhythmias may also exist.[126] Patients can also have

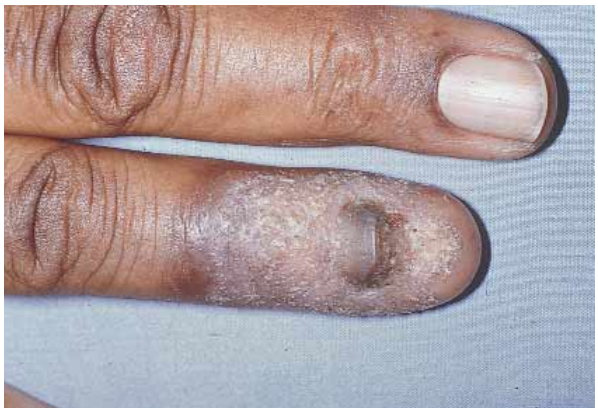

**Fig 11.** Finger and nail sarcoidosis.

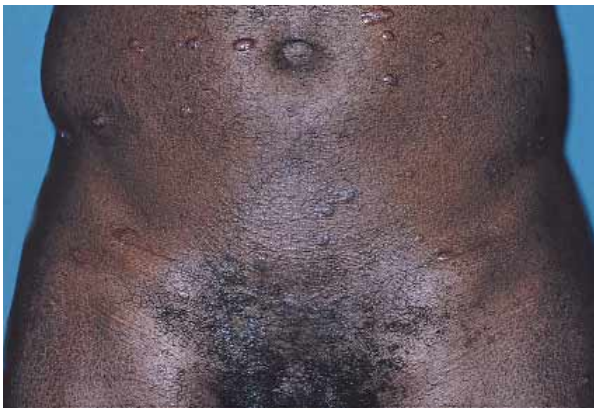

**Fig 13.** Inguinal adenopathy in the setting of nodular sarcoidosis.

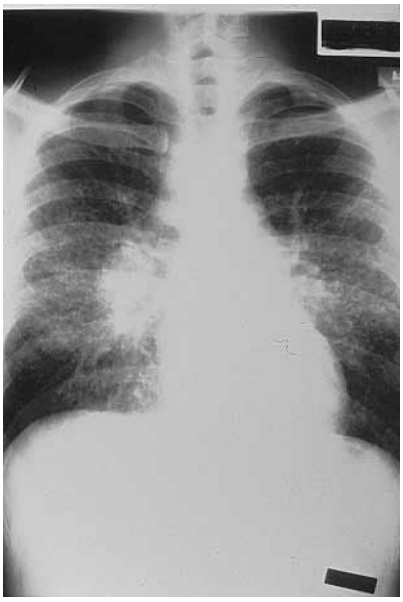

**Fig 12.** Stage II pulmonary sarcoidosis.

**Fig 14.** Lacrimal gland sarcoidosis.

papillary muscle dysfunction, infiltrative cardiomyopathy with congestive heart failure, and pericarditis.[125] Myocardial scintigraphy with thallium 201, echocardiography, 24-hour Holter monitor, and gallium 67 scan may be helpful in evaluating the extent of cardiac disease.[62,126,127]

Neurologic sarcoidosis manifests in 5% to 10% of sarcoidosis cases.[13,128,129] The most common is self-limited cranial nerve VII palsy, but all cranial nerves can be affected.[128,129] Other manifestations are aseptic meningitis,[130] sudden hearing loss,[131] seizure,[128,129] psychiatric changes,[128,129] arachnoiditis/perivasculitis,[132] space-occupying masses,[133] peripheral neuropathy,[133] stroke,[134] and myasthenia gravis.[135] Neurologic manifestations are associated with a higher mortality rate and can be either chronic or relapsing.[128,129,136] There is a case reported of neurosarcoidosis occurring after breast silicone implantation[137] and of the Uhthoff phenomenon (visual loss after exposure to heat) with sarcoidosis.[138]

Hypercalcemia is an endocrine manifestation of sarcoidosis occurring in up to 17% of cases.[139] Alveolar macrophage secretion of 1,25 dihydroxyvitamin $D_3$, independent of a feedback mechanism, induces increased calcium levels.[139] Johns and Michelle[15] noted anorexia, nausea, and vomiting from hypercalcemia caused by exposure to sunlight or ingested vitamin D. Supplemental oral calcium does not suppress granuloma vitamin $D_3$ production.[140] Diabetes insipidus can result from pituitary involvement.[141] Thyroid involvement can result in a diffuse or nodular goiter with hyperthyroidism.[142] Hashimoto's thyroiditis with elevated circulating thyroid autoantibodies can be seen in sarcoidosis.[143]

Renal sarcoidosis involvement can result in diffuse interstitial nephritis often without identifiable

granulomas.[15] These patients are at risk of renal insufficiency; however, patients with sarcoidosis have a 20% greater risk than the general population for the development of nephrolithiasis and nephrocalcinosis due to hypercalcemia.[144] There has been a report of bilateral hydronephrosis due to obstruction from a sarcoid retroperitoneal mass.[145] Sarcoidosis of the urethra can cause obstructive symptoms.[146]

Gastrointestinal sarcoidosis is rare. Involvement most commonly presents in the stomach as an ulcer or mass.[147] Dysphagia of solids and liquids has been reported,[148] as well as pancreatitis,[149] acute appendicitis,[150] and duodenal obstruction.[151]

Sarcoidosis granulomas may infiltrate virtually all organs including the breasts, uterus, fallopian tubes, ovaries, testicles, epididymis, and prostate gland.[85,152-55] Pearce and Nolan[154] reported a case of postmenopausal bleeding from endometrial granulomas. Sarcoidosis has also initially presented itself as a testicular mass. Carmody and Sharma[155] recorded 43 cases of intrascrotal sarcoidosis, 35% of which had unnecessary orchiectomy.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for systemic sarcoidosis includes foreign body granuloma, infection, autoimmune disorders, and neoplasia.[13] Lymphoma,[156] Wegener's granulomatosis,[157] primary biliary cirrhosis,[158] Churg-Strauss syndrome,[13] *M tuberculosis*,[13] atypical mycobacteria such as *M avium* and *M leprosum*,[159] histoplasmosis,[68] coccidioidomycosis,[68] brucellosis,[13] chlamydia,[160] tularemia,[68] *Treponema* and *Borrelia burgdorferi*,[161] as well as leishmaniasis[13] and toxoplasmosis[68] may give similar presentations to systemic sarcoidosis.

With foreign body reactions considered to be the cause of a systemic granulomatous process, the differential diagnosis includes talc, titanium, aluminum, zirconium, isocyanates, silicon, and beryllium.[13,68,162,163] Berylliosis is a chronic granulomatous disorder that closely mimics intrathoracic sarcoidosis. Distinguishing factors between the two disorders consist of the following: lack of EN (can have a nonspecific dermatitis) and ocular, cardiac, and extrathoracic manifestations with beryllium disease.[163] The major diagnostic difference is that the beryllium lymphocyte transformation test is abnormal in berylliosis and normal in sarcoidosis.[162,163] Berylliosis has a poor prognosis.[163]

The clinical and histopathologic differential diagnosis for specific classical cutaneous sarcoidosis consists of lupus vulgaris, leprosy, atypical mycobacterial infections, syphilis, localized foreign body reactions, tattoo-induced granulomatous reactions, necrobiosis lipoidica, granuloma annulare, granulomatous rosacea, metastatic Crohn's disease, deep fungal infection, cheilitis granulomatosis, and lupus miliaris disseminatus faciei.[68,164]

## CHILDHOOD SARCOIDOSIS

Infants and young children (9-15 years) present most frequently with lymph node, skin, joint, and eye involvement without the typical lung disease initially.[165] The classic presentation is with the triad of arthritis, skin lesions, and uveitis.[166] Spontaneous resolution occurs more often in children, but a significant number of small children have a residual morbidity.[165] It affects both sexes equally, and almost all children with sarcoidosis are symptomatic with vague complaints, including fever, weight loss, and fatigue.[167,168] Peripheral adenopathy is the most common presentation and the best site for biopsy if no cutaneous lesions are present.[165] A child with arthritis should have sarcoidosis included in the differential diagnosis.[109] The treatment of choice for childhood sarcoidosis is glucocorticoids.[168]

A rare autosomal dominant familial granulomatous, Blau syndrome, is similar to childhood sarcoidosis.[169] It presents with arthritis, uveitis, and skin lesions and has been linked to chromosome 16p12-q21.[170] It can be differentiated from sarcoidosis by family history and lack of pulmonary involvement.[170] Skin lesions were described as no more specific than "red dots" that have a similar histologic appearance to sarcoidosis.[169]

## SARCOIDOSIS SYNDROMES

Because of the many polymorphisms of sarcoidosis, there are several syndromes incorporating specific manifestations of the disease. Löfgren's syndrome, frequent in Irish, Scandinavian, and Puerto Rican female patients, consists of acute sarcoidosis, EN, migratory polyarthritis, fever, and iritis.[9,56,95,171] It usually has a good prognosis with a self-limiting course and resolution without therapy.[95] Sarcoidosis, Darier-Roussy type, is the presence of subcutaneous nodules of the trunk and extremities.[9] Heerfordt-Waldenström syndrome is the combination of fever, parotid enlargement, anterior uveitis, and facial nerve palsy.[9] Some complications of this syndrome can include lethargy, hyperalesia, papilledema, meningism, and other bizarre neurolgic manifestations.[95] Mikulicz's syndrome is bilateral sarcoidosis of the parotid, submandibular, sublingual, and lacrimal glands.[95,172]

## SARCOIDOSIS ASSOCIATIONS

Sarcoidosis has been found in association with autoimmune and neoplastic disorders as well as several medications. These disorders may be coinciden-

tal or represent true alliances.[12] Autoimmune disorders found in association with sarcoidosis are possibly related to the overall immune dysregulation with polyclonal B-cell production of antibodies found in sarcoidosis. The associations reported include autoimmune hemolytic anemia, autoimmune idiopathic thrombocytopenia, and Sjögren's syndrome[173]; systemic sclerosis, Sjögren's syndrome, and polymyositis[174]; insulin-dependent diabetes mellitus and ulcerative colitis[175]; vitiligo, autoimmune thyroiditis, and autoimmune chronic hepatitis[176]; autoimmune thyroiditis[143]; dermatitis herpetiformis[177]; acquired cutis laxa with dermatitis herpetiformis[178]; polyglandular autoimmune syndrome type II/III, autoimmune thyroid disease, insulin-dependent diabetes mellitus and celiac disease[179,180]; and dermatomyositis[181]; as well as systemic lupus erythematosus, rheumatoid arthritis, and spondyloarthropathies.[182] De Brandt et al[183] described 5 patients and Cox et al[184] described 7 patients with coexisting systemic sclerosis and sarcoidosis. They postulated that sarcoidosis should be considered in patients with systemic sclerosis who present with new pulmonary complaints.

Sarcoidosis can present simultaneously, before, or after chemotherapy for a malignancy.[185,186] Theories for such an association, according to a review of the literature by Pandha, Griffiths, and Waxman,[185] have included tumor cells releasing an antigenic substance, enhanced granuloma formation due to chemotherapy, or malignancy-induced susceptibility to an infectious agent. In the "sarcoidosis-lymphoma syndrome" the lymphoma develops after the onset of sarcoidosis.[156,187] Accentuation of cutaneous sarcoidosis during chemotherapy for the lymphoma has also been reported.[187] Hodgkin's lymphoma occurs most often with this association.[156] Additional types of lymphoproliferative disorders that are associated with sarcoidosis include non-Hodgkin's lymphoma, hairy cell leukemia, angioimmunoblastic lymphadenopathy with dysparaproteinemia, multiple myeloma, chronic lymphocytic leukemia, acute myelogenous leukemia, and acute lymphocytic leukemia.[188] Schmuth et al[189] reported sarcoidosis occurring in a patient after successful treatment for tumor-stage cutaneous T-cell lymphoma. Karakantza et al[156] suggested that sarcoidosis may be a predisposing factor because of the overall disturbance in the immune system. Sacks et al[190] found that patients with Hodgkin's disease and granulomatous reactions had a better prognosis than those without granulomatous reactions.

Other malignancy-sarcoid associations have been between sarcoidosis and testicular cancer,[191] carcinoid tumors,[192] bladder cancer,[193] melanoma,[194] Kaposi's sarcoma,[195] lung cancer,[196] and multiple myeloma.[197] Rayson, Burch, and Richardson[191] found testicular cancer to have the strongest association with sarcoidosis than any other cancer reported to date. Their computerized data search from 1950 to 1996 revealed a 100-fold increase for patients with sarcoidosis having testicular cancer then the general population. From 1962 to 1971 Brincker and Wilbek[198] observed 48 malignant tumors in 2544 patients with sarcoidosis. This was statistically significant when compared with the general population. Malignant lymphoma and lung cancer were seen in the greatest frequency. Romer, Hommelgaard, and Schou,[199] however, followed up Danish sarcoidosis patients for more than 20 years and found no increase in the incidence of any cancer.

Medication-induced sarcoidosis has been reported with interferon alfa therapy for hepatitis C[200,201] and chronic myelogenous leukemia[202] and with interferon beta therapy for multiple myeloma.[203] Ohhata et al[204] reported subcutaneous sarcoidal nodules at locations of subcutaneous interferon alfa injections.

Pouchot et al[205] reported 3 cases of Sweet's syndrome with mediastinal adenopathy associated with sarcoidosis. There have also been several cases of sarcoidosis in association with combined variable immunodeficiency. Patients will have signs and symptoms of sarcoidosis, but with hypogammaglobulinemia, recurrent infections, thrombocytopenia, and a predilection for splenic involvement.[206] Sarcoidosis has no adverse effect on pregnancy or fetal outcome, but can become exacerbated or lessen during this period.[207,208]

## DIAGNOSTIC EVALUATION

There is no diagnostic test for sarcoidosis; hence it is a diagnosis of exclusion. It is important to obtain a complete history with emphasis on occupational and environmental exposure. The emphasis during physical examination should be placed on the skin, lungs, eyes, nerves, and heart. If there are any abnormal findings suggestive of sarcoidosis, a biopsy (skin, peritracheal nodes, or salivary glands) should be performed to obtain histologic confirmation of noncaseating granulomas, polarization for foreign body evaluation, and tissue culture to rule out a bacterial, mycobacterial, and fungal origin. Bronchoscopy with transbronchial lymph node biopsy is often performed in patients without cutaneous involvement. At the time of bronchoscopy, bronchoalveolar lavage for evaluation of leukocyte differential counts may also be performed. A CD4/CD8 ratio higher than 3.5 is suggestive of sarcoidosis.[209]

Histologic examination of sarcoidosis shows well-demarcated islands of epithelioid cells with occasional

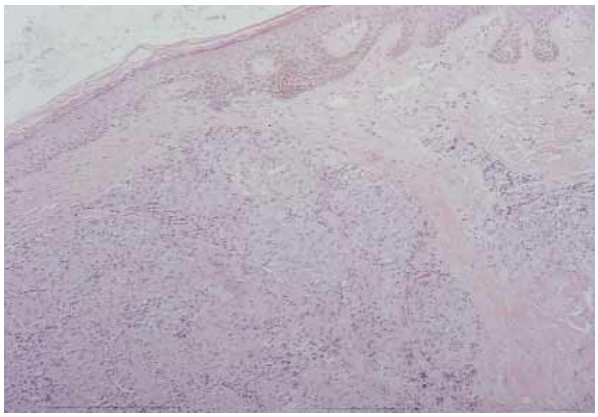

**Fig 15.** Sarcoidosis: Noncaseating granulomas.

giant cell formation and no necrosis (Fig 15).[12,68] Necrobiotic collagen is absent and there is sparse lymphocytic infiltrate concentrated peripherally around the noncaseating epithelioid granulomas.[68] Giant cells are more common in older lesions and often contain blue Schaumann's bodies (altered lysosomes) or stellate asteroid bodies (entrapped collagen).[68] These bodies, as well as the histologic findings noted above, are not specific for sarcoidosis.[12,68] Okamoto[210] noted epidermal changes in cutaneous sarcoidosis that contribute to the polymorphic cutaneous presentations. In 49 of the 62 cases studied, hyperkeratosis, acanthosis, parakeratosis, and epidermal atrophy were observed. In addition, Batres, Klima, and Tschen[93] described transepidermal elimination of sarcoidosis granuloma.

Radiographic diagnosis of sarcoidosis is done by chest radiography. Computed tomography of the chest is overutilized and does not affect the therapeutic treatment in these patients.[15] On the other hand, $^{67}$Ga gallium scans that demonstrated panda and/or lambda appearance in the face and chest, respectively, in sarcoidosis, can be used to help complement other diagnostic tools (Fig 16).[211] The panda appearance is the image of a face of a panda bear produced by parotid and lacrimal gland sarcoidosis granuloma gallium uptake.[212] The lambda sign is absorption by the bilateral hilar lymph node involvement and forms the Greek letter λ.[212] Lesions of nodular cutaneous sarcoidosis may be observed on gallium 67-labeled scanning with a differential diagnosis of cutaneous deep fungal and mycobacterial infections as well as cutaneous lymphomas.[213] Tschabitscher et al[214] showed technetium-99m–tetrofosmin scintigraphy to be useful in patients with suspected sarcoidosis. Eklund et al[215] found extrathoracic manifestations of sarcoid to be easier to detect for biopsy with somatostatin analogue scintigraphy.

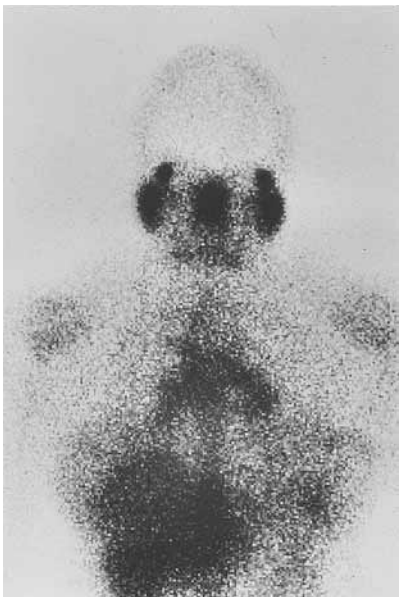

**Fig 16.** $^{67}$Ga scan from patient shown in Fig 1 demonstrating the panda and lambda signs.

Laboratory evaluation of a suspected patient with sarcoidosis includes liver and renal function tests, complete blood cell count, erythrocyte sedimentation rate, and determination of serum calcium and ACE levels. Other tests based on the clinical presentation may include rapid plasmin reagin and antineutrophil cytoplasm, antinuclear, antimitochondrial, and antithyroid antibodies. Additional clinical evaluation should include pulmonary function tests, electrocardiography, slit-lamp eye examination, and tuberculin/anergy testing.[9,13,56,216] The Kviem test is also included in this list of diagnostic tests for historical purposes. The Kviem test is a skin test in which the spleen or lymph node homogenate from a patient with sarcoidosis is injected intradermally to another patient with suspected sarcoid and later biopsy is performed to look for evidence of a sarcoid granuloma.[44,217] This test is not approved by the Food and Drug Administration.

Along with the diagnostic evaluation, specialists may also be consulted depending on the extent of organ involvement and any disease progression. Patients found to have sarcoidosis should also be routinely followed up for new organ involvement, disease progression, or development of a malignancy.

## MEASUREMENT OF DISEASE PROGRESSION

ACE is normally produced by endothelial cells in the kidney and in sarcoidosis by T-cell–stimulated epithelioid cells at the periphery of the granulomas.

ACE is not specific for sarcoidosis and is elevated in leprosy, alcoholic liver disease (cirrhosis), $\alpha_1$-antitrypsin deficiency, diabetes mellitus, Kaposi's sarcoma/HIV, Melkersson-Rosenthal syndrome, silicosis, hypersensitivity pneumonitis, Gaucher's syndrome, primary biliary cirrhosis, histoplasmosis, and asbestosis.[15,195,218,219] There is a false-positive rate of 10% and a false-negative rate of 40% when serum ACE levels are used to diagnose sarcoidosis.[1,220] Because elevated levels at times may correlate with radiologic and clinical abnormalities, ACE levels may be used as an adjunct, but not for specific diagnosis.[220] However, because of its variance in frequency, its absence in some cases of florid pulmonary disease, and its lack of correlation with the extent of cutaneous involvement, determination of ACE levels is generally not a useful guide for disease progression or therapeutic response.[1,44,221,222] Pulmonary function tests may be used to monitor patient's respiratory status, but gallium-labeled scans and bronchoalveolar lavage are not used routinely for monitoring disease progression.[9]

Many experimental techniques are available for measuring sarcoidosis disease progression. Ziegenhagen et al[223] found tumor necrosis factor $\alpha$ and serum IL-2 to be suitable parameters for predicting disease progression in patients who have no indication for therapy at the time of diagnosis. Serum level of soluble IL-2 receptors has been determined to be a serum marker of sarcoidosis inflammation.[224] Nakayama et al[225] suggested that serum TNF-receptor II levels may be useful parameters for monitoring the clinical course of sarcoidosis as well as being a marker for disease activity. Yokoyama et al[226] reported that 16 patients with chronic sarcoidosis had higher than normal serum IL-8 levels and proved this finding to be a good marker for monitoring disease activity. Takizawa et al[227] found that locally derived IL-6 and IL-8 were increased in sarcoidosis and showed a correlation with the activity of granulomatous lung disease. Bacchella et al[228] found serum procollagen I and III to be a disease marker for fibrosis in patients with sarcoidosis. Bansal et al[25] demonstrated elevated vitamin $D_3$, IL-10, and CD23 serum levels from patients with sarcoidosis. They theorized that IL-10 and vitamin $D_3$ levels contribute to the peripheral anergy seen in sarcoidosis. Increased levels of CD23 are suggestive of an increase in peripheral humoral immunity. Scheel-Toellner et al[229] found expression of CD26 to be suggestive of a $T_H1$ immune reaction. Shigehara et al[230] measured T-cell receptor $\gamma/\delta$ expression in the peripheral circulation and found that elevations may be useful for estimating disease activity of sarcoidosis. The $\alpha/\beta$ T-cell receptors are decreased in the peripheral circulation because of tissue compartmentalization of this component of the immune response. Hamblin et al[231] demonstrated mean circulating E-selectin levels to be 3 times higher in patients with sarcoidosis. Shijubo et al[232] suggested that serum intercellular adhesion molecule-1 is a useful blood marker to predict outcome and to monitor disease activity in sarcoidosis. Donghi, Giura, and Antonelli[233] found that increased serum copper in patients with mediastinal adenopathies is usually indicative of lymphomas, and the data also suggested that it can increase in nonneoplastic diseases such as sarcoidosis.

## TREATMENT

The indication for treatment of systemic sarcoidosis depends on disabling symptoms, organ derangement or dysfunction, and laboratory and ancillary study results.[9] Glucocorticoids are the first-line treatment.[13] In chronic disease nonsteroidal immunosuppressive agents are used to avoid long-term corticosteroid-induced side effects.[234] The agents most often used are antimalarials, methotrexate, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine.[3,62,234] The data on immunosuppressive agents are largely anecdotal (small series or case reports) and have not been proven to be efficacious by randomized placebo-controlled studies[3,13,234]; this is also true for therapies specific for cutaneous sarcoidosis. The indication for treating cutaneous sarcoidosis is disfigurement.[15] Because the skin may be the only noticeable sign of their disease, patients often seek treatment from the dermatologist.

Nonoral therapies reported for limited cutaneous sarcoidosis have included superpotent topical corticosteroids,[235] topical steroid with hydrocolloid occlusive dressing,[236] topical hydrocortisone 5% powder in hydrophilic ointment with phonophoresis,[237] intralesional triamcinolone (5-10 mg/mL repeated monthly),[238] intralesional chloroquine (50 mg/mL monthly),[239] and carbon dioxide or pulsed dye laser for lupus pernio.[240-243] Additional surgical approaches have consisted of dermabrasion, surgical excisions with grafting for ulcerative sarcoidosis, and plastic surgery for lupus pernio.[244,245]

Oral therapies for cutaneous sarcoidosis can be used for large disfiguring lesions, generalized involvement, or lesions that have proved refractory to localized nonoral therapies. Recently reported oral therapies that have been successful with cutaneous sarcoidosis include prednisone,[9,75,246] hydroxychloroquine,[247] chloroquine,[248] methotrexate,[246,249-251] allopurinol,[252-254] thalidomide,[255-258] isotretinoin,[259-260] PUVA,[246,261] tranilast,[262] melatonin,[263] and prospidine.[264] The use of other cyto-

toxic agents such as azathioprine and cyclophosphamide in cutaneous sarcoidosis is rarely mentioned in the literature.[3]

Although the precise mechanism of action of corticosteroids for sarcoidosis is unknown, Milburn et al[265] reported that corticosteroids restore the balance between locally produced $T_H1$ and $T_H2$ cytokines and immunoglobulin isotypes to normal levels in the sarcoid lung. The suggested dosage of prednisone for systemic sarcoidosis is 1 mg/kg for 4 to 6 weeks followed by a slow taper over 2 to 3 months.[9] Albertini, Tyler, and Miller[75] reviewed the cases of 16 patients treated with a prednisone dosage range up to 80 mg/day tapered over weeks to months based on response. Twelve patients had resolution of cutaneous findings and 4 patients had relapses after the dosage was tapered. Russo and Millikan[238] reported beneficial effects with alternate-day therapy with 30 mg of prednisone. A 30% to 50% efficacy is found with a daily or alternate-day dose of 200 to 400 mg of hydroxychloroquine.[3,238,247] Jones and Callen[247] found that 12 of 17 patients had regression of cutaneous lesions in 4 to 12 weeks with a hydroxychloroquine dosage of 2 to 3 mg/kg per day. Zic et al[248] recommend an initial 14-day course of 500 mg of chloroquine followed by 250 mg/day for long-term suppression of cutaneous sarcoidosis.

The use of methotrexate has increased in frequency for patients with chronic disease and may be useful against both skin and lung disease.[246,249-251] Although methotrexate is a potent immunosuppressive agent, its mechanism of action in sarcoidosis is unclear.[3] It is usually administered at 15 mg/week in 3 divided doses at 12-hour intervals.[238] Webster et al[249] described 3 patients with refractory sarcoidosis responding to 15 mg/week of methotrexate, ranging from 9 to 11 months of use with clearing of cutaneous lesions. For 2 years Baughman and Lower[234] followed up 17 patients with cutaneous sarcoidosis taking methotrexate; 94% of the patients noted improvement.

Allopurinol, 100 to 300 mg/day for several months, has been shown to be effective for cutaneous sarcoidosis.[238,252,253] Brechtel et al[253] reported that allopurinol 300 mg/day for 4 weeks cleared disseminated cutaneous sarcoidosis that had been refractory to chloroquine. Pfau et al[252] also found that scar sarcoidosis responded well to single-drug therapy of a daily dosage of 300 mg of allopurinol over a period of 4 to 7 months. Subcutaneous sarcoidosis with bone lesions was treated with 600 mg/day of allopurinol by Voelter-Mahlknecht et al[254]; however, at 6-month follow-up, oral steroids were indicated because of disease progression. The mechanism of action for allopurinol is unknown.

Low doses of thalidomide have proven to be effective in treating cutaneous sarcoid.[255-258] Thalidomide, used in treatment-resistant dermatoses, works via an inhibitory effect on cytokine production, specifically TNF-$\alpha$.[266] Thalidomide administered 200 mg/day for 2 weeks followed by 100 mg/day for 11 weeks, then 100 mg every other day was the dosage trial found to be effective in two patients with sarcoidosis that was unresponsive to corticosteroids.[257] Rousseau et al[255] used thalidomide in a patient whose disease had not responded to intralesional steroids, PUVA, hydroxychloroquine, oral steroids, and isotretinoin and noted a decrease in cutaneous inflammation for up to 1 year. Lee and Koblenzer[258] reported improvement of facial disfiguring cutaneous sarcoidosis using thalidomide (300 mg/day) for 4 months.

Patterson and Fitzwater[261] and Veien[246] reported the successful use of PUVA in hypopigmented and erythrodermic sarcoidosis, respectively. Georgiou et al[259] described one patient with cutaneous sarcoidosis who had complete remission with oral isotretinoin, 1 mg/kg per day for 8 months, with no recurrence or evidence of visceral involvement at 15-month follow-up. Waldinger et al[260] found 3 months of oral isotretinoin therapy to be effective in a patient with cutaneous sarcoidosis.

Cagnoni et al[263] reported the use of melatonin, 50 mg daily, in one patient with pulmonary and skin sarcoidosis for several months with clearance of skin lesions and improved pulmonary function. Yamada et al[262] treated two patients with tranilast and had resolution of skin lesions in 3 months. Tranilast is an antiallergy drug used for urticaria or atopy, which has antifibrotic properties but is not available in the United States.[262] In Russia, Samstov[264] reported the use of prospidine (an antitumor preparation with cytostatic effects) with corticosteroids in systemic sarcoidosis with involution of skin lesions.

## PROGNOSIS/MORTALITY

Up to 60% of patients with sarcoidosis experience spontaneous resolution, and an additional 10% to 20% of patients have resolution with corticosteroid use.[267] Patients with EN and acute inflammatory manifestations of sarcoidosis appear to have a high rate of spontaneous remissions (>80%).[58,60] The prognosis of cutaneous sarcoidosis depends on systemic involvement.[55] Relapses as treatment is withdrawn are frequent, especially in African American patients, who tend to have more severe and more prolonged symptoms than white patients.[15,267] The disease is chronic and progressive in 10% to 20% of patients, but only 1% to 5% of patients will eventually die of the disease.[62] Up to 10% of patients with cardiac and neu-

rologic disease will die of their illness.[268] Death from sarcoidosis is mostly due to failure of vital organs, specifically the lungs and heart.[13] Causes of death from sarcoidosis are pneumonia, pulmonary fibrosis leading to cor pulmonale and ventilatory failure, chronic obstructive pulmonary disease, cardiac arrhythmias, and sudden cardiac death.[126,218,269] Iwai et al[270] found 77% of 320 sarcoidosis deaths in Japan to be due to cardiac complications. In the United States, pulmonary complications account for greater mortality than cardiac sarcoidosis.[271]

Gideon and Mannino[271] did an extensive analysis of multiple-cause mortality data in the United States from 1979 to 1991. They found that of 26,866,600 people who died, 9014 had the diagnosis of sarcoidosis on their death certificates, and 5791 had died because of their sarcoidosis or related complications. Age-adjusted mortality rates were found to be consistently higher for African American than white patients, and within racial strata, mortality rates were higher for female than male patients. General rates were found to be 1.6/1,000,000 in 1979 to 2.1/1,000,000 in 1991. The mortality rates for male patients were found to be 1.3/1,000,000 in 1979 to 1.6/1,000,000 in 1991. The mortality rates for female patients were 1.9/1,000,000 in 1979 to 2.5/1,000,000 in 1991. The mortality rate for nonwhite/nonblack patients was found to be 0.5/1,000,000 overall. Mortality rates were found to vary by state; white patients had higher mortality rates in the northern states and black patients had higher mortality rates in the Middle Atlantic and northern Midwestern states. The lowest mortality rate was found to be in Hawaii.

ADDENDUM: Since submission of this manuscript for publication, Bachelez et al evaluated the safety and efficacy of minocycline in the treatment of sarcoidosis in a nonrandomized open study. Twelve patients with cutaneous sarcoidosis were treated with minocycline, 200 mg/day, for a median of 12 months. Eight patients were considered to have complete remission. Adverse reactions were minimal. Randomized controlled studies were recommended by the authors to evaluate the true efficacy of minocycline in these patients (Bachelez H, Senet P, Cadranel J, Kaoukhov A, Dubertret L. The use of tetracyclines for the treatment of sarcoidosis. Arch Dermatol 2001;137:69-73).

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## CME examination

Identification No. 801-105

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, English JC III, Patel PJ, Greer KE. J Am Acad Dermatol 2001;44:725-43.

*Directions for questions 1-14: Give single best response.*

1. The cause of sarcoidosis is
   a. *Mycobacterium tuberculosis*
   b. *Treponema pallidum*
   c. HIV
   d. oxalosis
   e. unknown

2. Which of the following countries matches the incidence of sarcoidosis in African American female patients in the United States?
   a. Sweden
   b. Japan
   c. Germany
   d. Bulgaria
   e. China

3. Which of the following inflammatory cells is the most important to granuloma formation in the skin?
   a. Platelets
   b. Neutrophils
   c. B-cell lymphocytes
   d. T-cell lymphocytes
   e. Eosinophils

4. Which of the following HLA types has been associated with a good prognosis in sarcoidosis?
   a. HLA-DR3
   b. HLA-A6
   c. HLA-B27
   d. HLA-CW4
   e. HLA-B13

5. Which of the following is not true of lupus pernio?
   a. Most commonly found in black women
   b. Indolent and indurated nasal skin changes
   c. Coexists with upper respiratory tract sarcoidosis
   d. Is a hallmark of fibrotic disease
   e. Most commonly found in white women

6. Which of the following cancers are most commonly associated with sarcoidosis?
   a. Multiple myeloma
   b. Testicular cancer
   c. Lung
   d. Malignant melanoma
   e. Breast

7. Which of the following is not a manifestation of musculoskeletal sarcoidosis?
   a. Bone cysts
   b. Myopathy
   c. Muscle nodules
   d. Tenosynovitis
   e. Osteosarcoma

8. What is the most debilitating ocular change in sarcoidosis?
   a. Iritis
   b. Blindness
   c. Photophobia
   d. Conjunctival nodules
   e. Blepharitis

9. What is the most common neurologic presentation in sarcoidosis?
   a. Peripheral neuropathy
   b. Sudden hearing loss
   c. Meningitis
   d. Cranial nerve VII palsy
   e. Hydrocephalus

10. The panda sign on $^{67}$Ga scanning in sarcoidosis refers to which of the following?
    a. Bilateral hilar node uptake
    b. Lacrimal/parotid gland uptake
    c. Bone uptake
    d. Liver uptake
    e. Spleen uptake

11. Sarcoidosis has been found in association with each of the following *except*
    a. systemic sclerosis
    b. lymphoma
    c. combined variable immunodeficiency
    d. interferon therapy
    e. methotrexate therapy

12. Berylliosis is characterized by which of the following?
    a. Erythema nodosum
    b. Iritis

c. Lupus pernio
d. Positive beryllium lymphocyte transformation test
e. Elevated serum angiotensin-converting enzyme level

13. To date, which of the following medications has not been used in the treatment of cutaneous sarcoidosis?
    a. Corticosteroids
    b. Methotrexate
    c. Hydroxychloroquine
    d. Thalidomide
    e. Tacrolimus

14. Age-adjusted mortality data for sarcoidosis revealed which of the following?
    a. Mortality rates are higher in white patients.
    b. Mortality rates have decreased since 1979.
    c. Mortality rates in northern states are higher in African American patients than in white patients.
    d. Female patients have a higher mortality rate.
    e. The lowest mortality rate in the United States is found in Arkansas.

*Directions for questions 15-18: For each of the numbered items choose the appropriate lettered item.*

a. Löfgren's syndrome
b. Darier-Roussy sarcoidosis
c. Heerfordt-Waldenström syndrome
d. Mikulicz's syndrome

15. Fever, parotid enlargement, uvietis, facial nerve palsy

16. Erythema nodosum, polyarthritis, fever, iritis

17. Subcutaneous nodules of the torso and extremities

18. Bilateral parotid, submandibular, sublingual, and lacrimal gland enlargement

*Directions for questions 19-24: For each of the numbered items choose the appropriate lettered item.*

a. True
b. False

19. Sarcoidosis affects all races, both sexes, and all ages.

20. Cases affecting African Americans are more often chronic and asymptomatic.

21. The incidence for African Americans in the United States is 35 to 64 per 100,000 population.

22. The exact origin is unknown.

23. Lasers have been reported as a treatment option for cutaneous sarcoidosis.

24. Asteroid bodies are a specific histologic finding in sarcoidosis.

*Directions for questions 25-30: For each of the numbered items choose the appropriate lettered item.*

a. True
b. False

25. Sarcoidosis is tuberculosis.

26. Polymerase chain reaction testing for detecting mycobacteria in sarcoidosis is inconclusive.

27. BCG vaccinations have decreased the incidence of sarcoidosis.

28. Polymerase chain reaction testing cannot distinguish between live or dead organisms.

29. *M tuberculosis* has been cultured from sarcoidal tissue.

30. Antituberculosis medication can cure sarcoidosis.

## Answers to CME examination

Identification No. 801-105

May 2001 issue of the Journal of the American Academy of Dermatology

Questions 1-30, English JC III, Patel PJ, Greer KE. J Am Acad Dermatol 2001;44:725-43.

1. e
2. a
3. d
4. a
5. e
6. b
7. e
8. b
9. d
10. b
11. e
12. d
13. e
14. d
15. c
16. a
17. b
18. d
19. a
20. b
21. a
22. a
23. a
24. b
25. b
26. a
27. b
28. a
29. b
30. b

**AMERICAN BOARD OF DERMATOLOGY EXAMINATION DATES**

In 2001, the Certifying Examination of the American Board of Dermatology (ABD) will be held at the Holiday Inn O'Hare International in Rosemont, Illinois on Oct 14 and 15, 2001. **The deadline for receipt of applications is May 1, 2001.**

The next examination for subspecialty certification in Dermatopathology will be held in Tampa, Florida on Friday, Nov 16, 2001. **The deadline for receipt of applications is July 1, 2001.**

The next examination for subspecialty certification in Clinical and Laboratory Dermatological Immunology will be held in Rosemont, Illinois, on Oct 12, 2001.

The next Recertification Examination of the ABD will be mailed to approved candidates on June 1, 2001.

A certification process is being developed for the subspecialty of Pediatric Dermatology. It is anticipated that the first examination will be administered in 2002 or 2003. Further details about the examination will be available from the Board office.

For further information about these examinations, please contact:

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