

Sarcoidosis

Clinical Presentation, Immunopathogenesis, and Therapeutics

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CASE PRESENTATION

A black woman in her sixth decade presented 8 years earlier with a chronic nonproductive cough, dyspnea, and fatigue and was suspected to have sarcoidosis. An inguinal lymph node biopsy demonstrated noncaseating granulomas. A subsequent transbronchial lung biopsy excluded infection and confirmed sarcoidosis. She was treated with 2 courses of oral prednisone, lasting approximately 3 months each. She was reluctant to continue this therapy because of associated mood changes. Approximately 6 years after diagnosis, she sought specialty care for progressive fatigue, dyspnea on exertion, and a chronic, nonproductive cough. During the evaluation, she was found to have a reduced platelet count; aside from the finding of splenomegaly, a hematological workup for thrombocytopenia was nondiagnostic.

Physical examination established a normal resting room air pulse oximeter oxygen saturation of 95% and mild bilateral expiratory wheezes. Laboratory testing reconfirmed thrombocytopenia (platelet count: $69 \times 10^3/\mu\text{L}$

Sarcoidosis is a multisystem granulomatous disorder that most often affects the lungs and may cause significant morbidity. Sarcoidosis can manifest as neurological disease, uveitis, blindness, end-stage pulmonary fibrosis, pulmonary hypertension, dysrhythmias, cardiomyopathy, hypercalcemia, and renal failure. Sarcoidosis persists as chronic disease in approximately one-third of those affected. Clinical pitfalls and misconceptions about the course of disease place this population at risk for delayed or inadequate care. While noncaseating granulomas are the histopathological hallmark of sarcoidosis, they also are nonspecific. No pathognomonic diagnostic test exists for sarcoidosis, so the diagnosis remains one of exclusion. While the etiology of sarcoidosis is still unknown, recent insights into its immunopathogenesis have moved investigators closer to finding more effective treatments. Corticosteroids remain the standard of care when treatment is indicated, despite their adverse effect profile. Clinical investigations of novel drugs and biological agents targeting mechanisms involving CD4 type 1 helper T cells may provide more effective, better tolerated therapies.

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[range: $173\text{--}369 \times 10^3/\mu\text{L}$]; to convert to $\times 10^9/\text{L}$, multiply by 1) and an elevated serum angiotensin-converting enzyme level (232 U/L [range: 16-52 U/L]; to convert to nkat/L, multiply by 16.667). Pulmonary function testing demonstrated moderate restriction (total lung capacity: 2.33 L, which is 65% of the predicted level) and severe diffusion impairment (4.86 mL/min/mm Hg, which is 26.8% of the predicted level). The 6-minute walk test showed a reduced walk distance (439 m) and oxygen desaturation to 76%. A standard chest computed tomographic scan and prone high-resolution computed tomographic scan (FIGURE 1) revealed marked intersti-

tial thickening, cystic changes predominantly affecting the upper lobes, mild mediastinal adenopathy, and splenomegaly. Supplemental oxygen was initiated along with prednisone (30 mg/d). She experienced an improvement in

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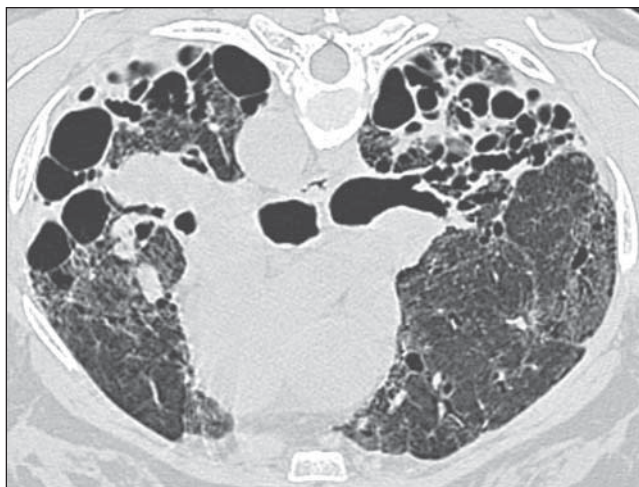
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See also Patient Page.



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Figure 1. High-Resolution Chest Computed Tomography (HRCT)

The HRCT was performed on a black woman in her sixth decade with untreated pulmonary sarcoidosis. It reveals extensive cystic changes involving the upper lobes, bilaterally, as well as severe, interstitial thickening and fibrosis, reflecting stage IV pulmonary sarcoidosis.

cough, dyspnea, and fatigue, and subsequently self-tapered and discontinued prednisone after approximately 6 months. She reported feeling depressed.

Epidemiology

In 1899, Boeck¹ coined the term sarcoidosis to name his findings of “epithelioid cells with large pale nuclei and also a few giant cells” found on skin biopsy. Sarcoidosis can affect individuals at all ages, but most commonly affects those in the third to fourth decades of life.² In the United States, the adjusted annual incidence rate among blacks is roughly 3 times that among whites (35.5 cases per 100 000 population vs 10.9 per 100 000 population, respectively).² In blacks, sarcoidosis is more likely to be chronic and fatal.³

Because sarcoidosis most commonly involves the skin, eyes, and the lungs, the cause of sarcoidosis is presumed to be airborne. Despite a large, well-matched, multicenter, etiologic study, no single predominant, environmental, or occupational factor has been identified, although modest risk was found for exposure to moldy environments (odds ratio, 1.61; 95% confidence

interval, 1.13-2.31) and insecticides (odds ratio, 1.52; 95% confidence interval, 1.14-2.04).⁴

Manifestations

Patients often report a prolonged workup prior to receiving the diagnosis of sarcoidosis.⁵ Judson et al⁵ reported that the diagnosis of sarcoidosis was made on the first physician visit in only 15.3% of cases. The presence of pulmonary symptoms was associated with a delayed diagnosis, often exceeding 6 months.

Thoracic involvement occurs in more than 90% of patients with sarcoidosis. Symmetrical hilar adenopathy is the most common thoracic manifestation. Unilateral hilar adenopathy occurs in only 3% to 5% of patients. Mediastinal lymphadenopathy without hilar lymph node enlargement is rare and points to an alternative diagnosis. Pulmonary function tests yielding abnormal results most often demonstrate a decreased diffusion capacity and a restrictive ventilatory defect. At least 50% of patients also have obstructive airways disease.³ Pulmonary hypertension occurs in 6% to 23% of patients at rest and in more than 40% of patients during exercise.⁶ Pulmonary hypertension com-

plicates pulmonary sarcoidosis more frequently in advanced parenchymal disease and significantly worsens prognosis.⁷

While the thorax is the most common site of disease, skin involvement occurs in at least 30% of patients and is often missed. Cutaneous sarcoidosis presents as single foci or crops, and is often attributed to other causes, perhaps because of its highly variable manifestations (eg, macular-papular, nodular, psoriatic-like, and hypomelanotic). Careful skin examination is warranted because biopsy of a sarcoidal lesion has a high diagnostic yield. Erythema nodosum occurs more commonly in women and portends a good prognosis during an acute presentation.

Eye involvement, including any ocular element potentially affected, occurs in about 25% of patients. The presence of ocular sarcoidosis may precede the actual diagnosis by years or even decades. The more insidious-presenting chronic anterior uveitis is more common than the acute pain and photophobia of acute anterior uveitis. Thus, examination with a slit lamp to identify the waxy precipitates of inflammatory cells is essential in the initial evaluation of patients who may have sarcoidosis.⁸

Cardiac sarcoidosis is much more common than clinically appreciated⁹ and is found at autopsy in up to 25% of patients in the United States¹⁰; in Japan, the incidence is greater than 50%. Cardiac sarcoidosis can affect any part of the heart and conduction system. Sarcoidal granulomas and subsequent fibrosis may induce complete heart block and ventricular arrhythmias. Patients may present with syncope, heart failure, or sudden death. No well-studied approach to screen for cardiac sarcoidosis exists. Screening at presentation should consist of a detailed medical history, physical examination, and an electrocardiographic examination. Abnormal physical or electrocardiographic findings or suggestive symptoms should prompt further evaluation, which may

include an echocardiogram, cardiac event monitoring, and further imaging.⁹ Positron emission tomographic (PET) scanning may be the most sensitive test.¹¹ Delayed-enhancement cardiac magnetic resonance imaging may detect minute amounts of sarcoid-related cardiac damage, and may be more widely available and less costly than PET.¹² In addition, anti-inflammatory agents may reduce fluorodeoxyglucose uptake, and theoretically reduce PET sensitivity. While electrophysiological studies should be used to evaluate patients with syncope or significant electrocardiographic abnormalities, the sensitivity and ability to stratify patients by risk is poorly defined. A normal electrophysiological study at any one point does not preclude future granulomatous infiltration and fibrosis in critical regions. Because cardiac sarcoidosis often occurs in the absence of apparent disease elsewhere, sarcoidosis should be considered in any nonischemic form of cardiomyopathy, particularly when rhythm disturbances are prominent.

Neurosarcoidosis is detected at autopsy in up to 25% of patients and can occur in the absence of apparent disease elsewhere. Neurological disease precedes the diagnosis of sarcoidosis in up to 74% of patients, and is the only manifestation in 10% to 17% of patients with sarcoidosis.¹³ Any part of the nervous system may be affected, although cranial nerve involvement is the most common form. Of the cranial nerves, the facial and optic nerves are most commonly involved. Pituitary involvement generally presents with diabetes insipidus, and hypothalamic involvement can cause pituitary insufficiency.¹⁴ Spinal cord involvement with paraplegia and quadriplegia is well recognized and portends a poor prognosis. Other common symptoms of neurosarcoidosis include ataxia, cognitive dysfunction, headache, seizures, and weakness.¹⁵

Depression and neuropsychiatric illness often accompany pulmonary sar-

coidosis. The incidence of depression has been reported to be between 13% and 66%. The multicenter ACCESS (A Case Control Etiologic Study of Sarcoidosis) trial found that 46% of patients reported symptoms of depression compared with 27% of controls.¹⁶ A lower quality of life has been associated with increased dyspnea and with oral corticosteroid use. These studies point to the need for greater attention to this serious comorbidity and consideration for a multidisciplinary management approach.

Diagnostic Pathway

The diagnosis of sarcoidosis is supported by a compatible clinical and radiographic presentation, and histological evidence of noncaseating granulomas on biopsy (without organisms or particles). In patients who present with Lofgren syndrome (erythema nodosum, hilar adenopathy, and polyarthralgias), a probable diagnosis of sarcoidosis can be made without biopsy. In all other cases, a biopsy should be performed on the most accessible organ, such as the skin or peripheral lymph nodes. A bronchoscopy along with a transbronchial biopsy has a diagnostic yield of 85% and is useful even in patients with hilar lymphadenopathy alone based on chest x-rays with Scadding stage I. The high diagnostic yield of endobronchial ultrasound-guided fine needle aspiration of intrathoracic lymph nodes¹⁷ makes the use of mediastinoscopy mostly unnecessary. Several reports have demonstrated the value of PET scanning to detect occult disease, which may help to determine an accessible site for biopsy, particularly in difficult cases such as cardiac or neurological involvement.¹⁸

Prognosis and Treatment

Remission occurs for more than half of patients within 3 years of diagnosis, and within a decade for two-thirds with few or no consequences. Unfortunately, up to one-third of patients have persistent disease, leading to significant organ impairment. Less than 5% of pa-

tients die of sarcoidosis, with death usually the result of cardiac or neurological involvement, or respiratory failure due to pulmonary fibrosis. Corticosteroids remain the principal treatment. Both high-dose corticosteroids for prolonged periods, and a burst-and-taper approach as used for asthma, should be avoided. In general, 6 to 9 months of treatment is required. Expert opinion recommends a dosing schedule of 30 to 40 mg/d of prednisone with a biweekly taper of 5 mg/d until 10 to 20 mg/d is reached and maintained for a few months. Several alternatives can be considered for those who do not tolerate corticosteroids.¹⁹

Many individuals with sarcoidosis require no treatment. For pulmonary sarcoidosis, there is no general consensus regarding which subgroups require treatment, the treatment type and dose, or duration of therapy; even among experts, there are few areas of agreement.²⁰ The decision to initiate treatment depends on the site and severity of organ involvement (TABLE 1). In pulmonary sarcoidosis, therapy is often started for troublesome symptoms, such as an intractable cough or dyspnea on exertion, or for progressive pulmonary function deterioration. There is somewhat greater consensus regarding the treatment of cardiac, ocular, and neurosarcoidosis; however, there is no therapy approved by the US Food and Drug Administration for sarcoidosis.

Genetics

Familial clustering of sarcoidosis has been well described.²¹ Having a first-degree relative with sarcoidosis increases the risk for disease by 5-fold.²² However, less than 1% of all first-degree relatives of patients with sarcoidosis have the disease, so screening for sarcoidosis among relatives is not warranted. Genome-wide scanning for sarcoidosis susceptibility genes has identified a few candidate genes.^{23,24} One identified candidate gene, butyrophilin-like 2, has been replicated in more than 1 population.^{25,26} Its role in sarcoidosis awaits further studies.

Table 1. Approach to Treating Individual Organ Systems^a

	Treatment		
	Not Generally	Sometimes	Generally
Clinically active disease			
Neurological	No	No	Yes
Ocular	No	No	Yes
Cardiac	No	No	Yes
Renal	No	No	Yes
Hepatic	No	Yes	No
Splenic	No	Yes	No
Pulmonary			
Stage 0	Yes	No	No
Stage I	Yes	No	No
Stage II	No	Yes	No
Stage III	No	Yes	No
Stage IV	No	Yes	No
Cutaneous	No	Yes	No
Musculoskeletal	No	Yes	No
Comorbid conditions			
Depression	No	No	Yes
Fatigue	No	Yes	No
Pulmonary hypertension	No	No	Yes

^aTreatment is dependent on site and severity of organ involvement. In pulmonary sarcoidosis, therapy is often initiated for significant symptoms and/or for functional deterioration. For cardiac disease and neurosarcoidosis, therapy is essential. Treatment with doses higher than those used in patients with pulmonary sarcoidosis are generally required.

Immunopathogenic Mechanisms

Sarcoidosis is a multisystem inflammatory disease of undetermined etiology, characterized by T-lymphocyte infiltration, granuloma formation, and distortion of normal microarchitecture. Sarcoidosis results from an uncontrolled cell-mediated immune reaction, manifested by well-formed, noncaseating epithelioid granulomas.¹⁹ Immunological findings, such as a restricted repertoire of T-cell receptors and oligoclonal T-cell expansion, suggest selective activation of the immune system and stereotypically acquired and innate immunoresponses. Serum amyloid A may play an important role in the innate immune response in chronic sarcoidosis (FIGURE 2).²⁷ The prevailing theory holds that sarcoidosis develops in genetically predisposed hosts from a cell-mediated immune response to 1 or more unidentified antigens.²⁸ Mycobacteria and propionibacteria have been identified as possible causative agents. Mycobacterial tuberculosis catalase-peroxidase protein was identified in approximately 50% of sarcoidosis tissues sampled in a 2005 study.²⁹

Granuloma Formation

Immune granulomas have a central follicle composed of epithelioid and CD4 type 1 helper T cells (T_H1) surrounded by a ring of fibroblasts, B cells, and CD8 T lymphocytes. Activated tissue macrophages resemble epithelial cells (hence the term, epithelioid granulomas); these cells become the primary sources for angiotensin-converting enzyme.

Granuloma formation can be divided into 4 stages: initiation, accumulation, effector phase, and resolution (Figure 2).³⁰ During initiation, macrophages and monocytes are the first cells to be recruited. Antigens are internalized by macrophages, which then process and present peptides to CD4 T cells via class II major histocompatibility complex molecules (FIGURE 3).³¹ Interactions between macrophages and T cells are essential for T-cell activation and initiation and development of granulomas. Co-stimulatory molecules CD80, CD83, CD86, and HLA-DR play an important role in the interface between antigen-presenting cells

and T cells. Following recruitment, T cells and macrophages release mediators that further amplify the T_H1 response, leading to greater proliferation and recruitment. During the final phase (resolution), there is an increased production of macrophage-generated cytokines favoring fibrosis (eg, transforming growth factor β).³²

T-Cell Activation and Signaling

T lymphocytes may be activated via several mechanisms, including T-cell receptor complexes, toll-like receptors, and cytokine or chemokine receptors (Figure 3); the latter are upregulated in both acute and chronic inflammation. Cytokines and chemokines not only activate CD4 T_H1 cells, but also play important roles in recruitment and migration. Chemokines are small peptide cytokines, which attract leukocytes and influence their behavior.

The T-cell receptor complex is comprised of clonally variable antigen-binding chains (α and β) and invariant signaling proteins. Antigens binding to the T-cell receptor commences protein tyrosine kinase activation that is mediated by kinase families. The first phase of protein tyrosine phosphorylation triggers subsequent signaling pathways (Figure 3), such as mitogen-activated protein kinase, protein kinase C, and increased intracellular free calcium. These downstream pathways in turn activate transcription factors such as activating protein 1 and the nuclear factor of activated T cells, which promote gene expression that controls T-cell proliferation, differentiation, apoptosis, and anergy.

Toll-like receptor binding with bacterial or viral products propagate intracellular signaling cascades via mitogen-activated protein kinases and nuclear factor κ B (NF- κ B). This leads to translocation of transcription factors, such as NF- κ B, activating protein 1, and nuclear factor of activated T cells to the nucleus, which induces the transcription of genes encoding pro-

inflammatory chemokines and cytokines. In addition, NF- κ B, nuclear factor of activated T cells, and activating protein 1 induce new gene transcription that leads to T-cell differentiation, proliferation, and effector functions. These T-lymphocyte signal transduction pathways are potential therapeutic targets in sarcoidosis.

Cytokines and Chemokines

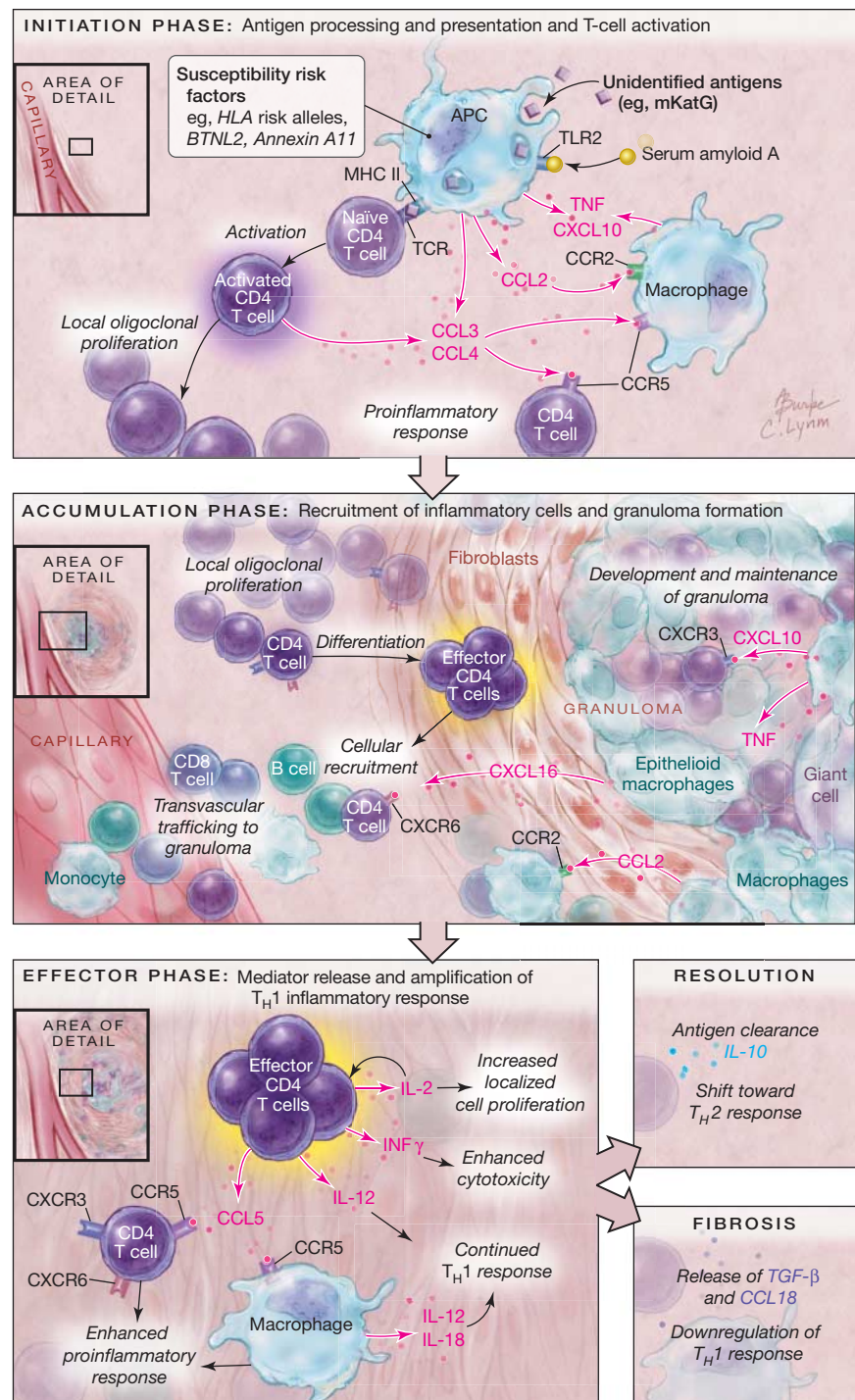
In sarcoidosis, T_H1 cells spontaneously release increased amounts of interleukin 2 (IL-2) and interferon γ (IFN- γ).^{33,34} Interleukin 2 acts as a local growth factor for T lymphocytes, whereas IFN- γ enhances the accessory and cytotoxic functions of T cells and regulates the secretion of other lymphokines. Tumor necrosis factor (TNF), IL-12, and IL-18 play critical roles in driving commitment of T_H1 cells. Interleukin 12 and IL-18 induce IFN- γ production and enhance T-cell cytotoxicity.³⁵ Chemokine regulation on activation normal T-cell expression and secretion (RANTES or CCL5), macrophage inflammatory protein 1 β (MIP-1 β or CCL4), monocyte chemoattractant protein 1 (MCP-1 or CCL2), and IFN- γ -inducible protein 10 (CXCL10) are expressed in sarcoid granulomas and enhance the migration of effector cells.^{30,36} Interactions between chemokines and receptors that activate mitogen-activated protein kinase pathways play a major role in inflammation and T-cell responses (Figure 3).

Clinical Trials

Despite the dearth of long-term efficacy data and numerous adverse effects, corticosteroids remain the standard of care. More effective, better-tolerated therapies are needed. Agents modulating key CD4 T_H1 cell activities (TABLE 2) may have salutary effects. It remains to be seen whether B-cell inhibition has a role in the treatment of sarcoidosis (NCT00855205).

Methotrexate, an antimetabolite, interferes with DNA synthesis, repair, and cellular replication via reversible inhibition of dihydrofolate reductase. Methotrexate also inhibits another

Figure 2. Proposed Mechanisms of Sarcoid Granuloma Formation



In a genetically predisposed host, antigen presentation leads to CD4 T-cell activation, downstream clonal proliferation, and elaboration of type 1 helper T cytokines or chemokines. This promotes cellular accumulation and nidus formation, resulting in granuloma. APC indicates antigen-presenting cell; *BTNL2*, butyrophilin-like protein 2 gene; CCL, chemokine (C-C motif) ligand; CCR, chemokine (C-C motif) receptor; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; MHC II, major histocompatibility complex II; mKatG, *Mycobacterium tuberculosis* catalase-peroxidase protein; TCR, T-cell receptor; TGF- β , transforming growth factor β ; TLR, toll-like receptor; TNF, tumor necrosis factor.

enzyme, which results in increased concentrations of adenosine (a potent anti-inflammatory mediator). Methotrexate inhibits cell-mediated immune responses and has been used to treat other granulomatous diseases. The mechanism of action of methotrexate in sarcoidosis is unknown, but may involve both cytotoxic and anti-inflammatory effects; the latter may in part be related to suppression of TNF and increased extracellular adeno-

sine.³⁷ In a randomized, double-blind, placebo-controlled trial, 24 patients with acute sarcoidosis received placebo or methotrexate to determine methotrexate's steroid-sparing effect.⁴⁹ At 12 months, the patients who received methotrexate required significantly less prednisone than the patients in the placebo group (8.3 mg/d vs 16 mg/d of prednisone, respectively; $P < .001$). Methotrexate appears to be a steroid-sparing agent;

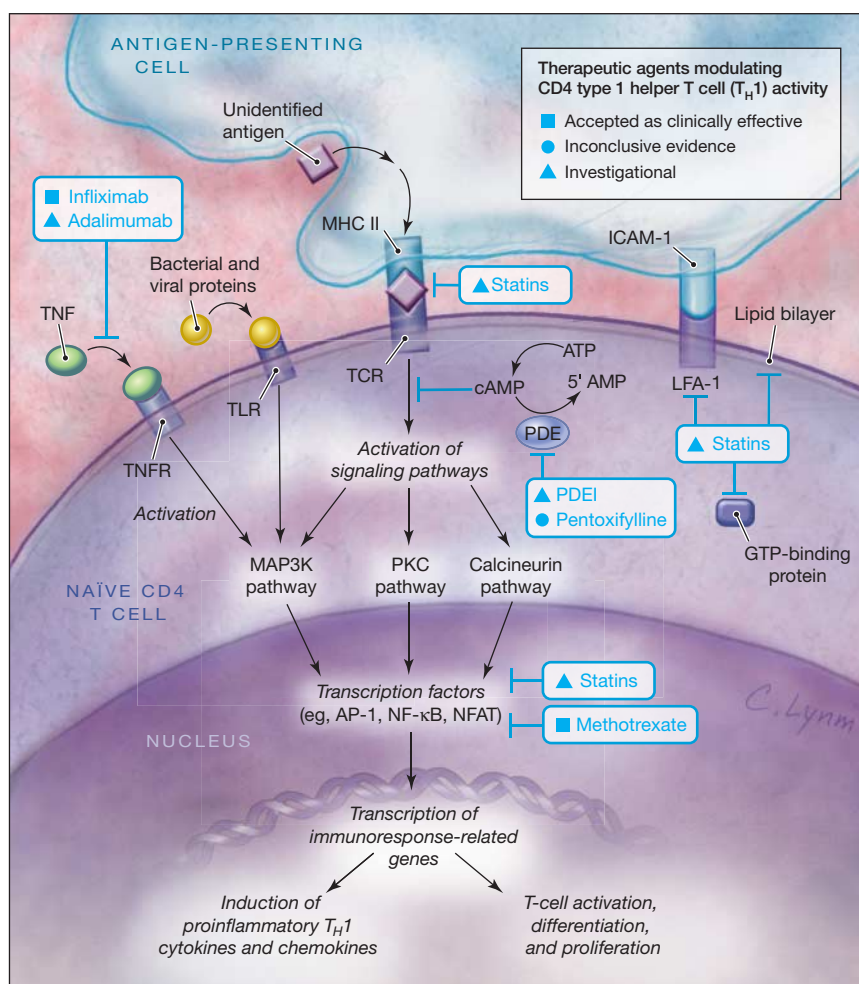
however, larger studies are required for validation.

Tumor necrosis factor is an important cytokine in granulomatous inflammation, and it exerts its action at multiple cellular and subcellular sites. Selective inhibition of TNF has been investigated as a treatment strategy for sarcoidosis. Etanercept (a dimeric fusion protein) binds TNF and neutralizes it by preventing interaction with cell-surface TNF receptors. In an open-label study with etanercept (dose: 25 mg/d twice weekly), no clinical benefit and no decrease in serum or bronchoalveolar lavage TNF levels were demonstrated.⁴⁸ Using a similar strategy, infliximab (a chimeric monoclonal antibody that inhibits TNF) was investigated in a multicenter randomized, double-blind, placebo-controlled trial. A total of 138 patients received infliximab (3 or 5 mg/kg) or placebo. The patients in the infliximab groups (3 or 5 mg/kg) had a mean increase of 2.5% from baseline to week 24 in the percentage of predicted forced vital capacity compared with no change in patients treated with placebo ($P = .04$).³⁸ There were no significant differences between the treatment groups for any of the major secondary end points. While the role of infliximab in pulmonary sarcoidosis remains unclear, the results of this study support further evaluation of anti-TNF therapy in active pulmonary sarcoidosis. There is a study under way for adalimumab (a TNF inhibitor) as a treatment for cutaneous sarcoidosis (NCT00274352).

Cyclosporine is a lipophilic, calcineurin inhibitor, which impedes T-lymphocyte activation and produces calcium-dependent, reversible transcription inhibition of IL-2, and decreases IL-6 and IFN- γ synthesis. Clinical trials with cyclosporine in pulmonary sarcoidosis have not shown benefit.^{46,47}

The cyclic nucleotides (adenosine 3' 5' cyclic monophosphate and guanosine 3' 5' cyclic monophosphate) are important intracellular second messengers that regulate multiple critical pathways. Concentrations of adenosine 3' 5' cyclic monophosphate and guanosine 3' 5' cyclic monophosphate are

Figure 3. T-Cell Signaling and Targets in Sarcoidosis



T-cell activation may occur via the T-cell receptor (TCR), toll-like receptor (TLR), cytokine or chemokine receptors, leading to signal transduction and activation of transcription factors, which promote gene expression controlling T-cell proliferation, differentiation, apoptosis, anergy, and production of proinflammatory cytokines and chemokines. Sites of action of therapies are shown in blue rectangles (see also Table 2). AMP indicates adenosine monophosphate; AP-1, activator protein 1; ATP, adenosine triphosphate; cAMP, adenosine 3' 5' cyclic monophosphate; GTP, guanosine triphosphate; ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; MHC II, major histocompatibility complex II; MAP3K, mitogen-activated protein kinases; NFAT, nuclear factor of activated T cells; NF- κ B, nuclear factor κ B; PDE, phosphodiesterase; PDEI, phosphodiesterase inhibitors; PKC, protein kinase C; TNF, tumor necrosis factor; TNFR, TNF receptor.

Table 2. Potential Therapies for Sarcoidosis

Serious Adverse Effects and Warnings			
	Key Mechanisms	US FDA Boxed Warning	General Warnings
Accepted as Effective			
Methotrexate ^{37,a}	Interferes with dihydrofolate reductase, increases AICAR, and increases concentrations of adenosine, which has numerous anti-inflammatory effects May suppress TNF activity via inhibition of TNF-induced activation of NF-κB	Myelosuppression (fatalities reported) Interstitial pneumonitis (reported with doses ≥7.5 mg/wk; not always fully reversible) Immunosuppression Hepatic inflammation, cirrhosis, or necrosis Renal dysfunction Gastrointestinal tract toxicity, including perforation Lymphoma (may occur with low dose) Severe dermatologic reactions (fatalities reported) Pregnancy category X (fetal death and anomalies)	Monitor closely to detect adverse effects early Complete blood counts monthly Renal and liver function tests every 1-2 mo Caution required with concurrent administration of certain drugs (eg, NSAIDs, salicylates, and penicillins) Transient liver function test abnormalities are common Consider relatively low doses in older patients
Infliximab ³⁸	Inhibits TNF by binding to the soluble and transmembrane forms Inhibits the binding of TNF to its receptors	T-cell lymphoma and leukemia risk Serious infection risk (tuberculosis, fungal)	Hypersensitivity infusion reactions Lupus-like syndrome CHF decompensation Cytopenias Hepatotoxicity Pregnancy category B
Inconclusive Evidence			
Pentoxifylline ³⁹⁻⁴¹	Inhibits phosphodiesterase and leads to increased intracellular adenosine monophosphate Inhibits TNF	None	Use in patients with recent cerebral or ocular hemorrhage Pregnancy category C
Investigational ^b			
Anti-CD20 antibodies	Inhibits CD20 and depletes B cells Fc receptor γ-mediated antibody-dependent cytotoxicity	Infusion reactions (fatalities reported) Progressive multifocal leukoencephalopathy (fatalities reported) Severe mucocutaneous reactions (fatalities reported)	Cardiac arrhythmias and angina Severe infections Hepatitis B reactivation (fatalities reported) Bowel obstruction and perforation Severe cytopenias Pregnancy category C
Statins ⁴²⁻⁴⁴	Interfere with HMG CoA reductase and decreases isoprenylation of small G proteins Interferes with MHC II and LFA-1 Interferes with T-cell activation via disruption of the lipid bilayer on T cells	None	Liver dysfunction Rhabdomyolysis Myalgias Pregnancy category X
Phosphodiesterase inhibitors ^{39,45}	Inhibits phosphodiesterase and leads to increased intracellular adenosine monophosphate ^c	Not approved for clinical use in the United States	Pregnancy category to be determined
Considered Clinically Ineffective for Pulmonary Sarcoidosis			
Cyclosporine ^{46,47}	Inhibits calcineurin Alters LFA-1 and ICAM-1 expression Interferes with T-cell activation, IL-2 gene transcription, and reduces production of several other cytokines Inhibits activation and/or maturation of cells involved in cell-mediated immunity	Increased risk of lymphoma and other neoplasia Increased infection risk	Hypertension Nephrotoxicity Pancreatitis Hepatotoxicity Hemolytic uremic syndrome Posttransplant lymphoproliferative disorder Pregnancy category C No role as first-line therapy in pulmonary sarcoidosis (based on expert consensus)
Etanercept ⁴⁸	Binds to TNF, preventing its interaction with cell surface receptors	Lymphoma and other malignancies Serious infection risk (tuberculosis, invasive fungal, opportunistic infections)	Hypersensitivity infusion reactions CHF decompensation Cytopenias or anemias Hepatotoxicity Demyelinating disease, exacerbation, or new onset Hepatitis B virus carrier reactivation Pregnancy category B Not to be used for sarcoidosis (based on expert consensus) unless future studies demonstrate a favorable risk to benefit profile

Abbreviations: AICAR, aminoimidazolecarboxamidoadenosine ribonucleotide transformylase; CD20, cluster of designation 20; CHF, congestive heart failure; FDA, Food and Drug Administration; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A reductase; ICAM-1, intercellular adhesion molecule 1; IL-2, interleukin 2; LFA-1, leukocyte function-associated antigen 1 (also known as CD11a/CD18 and $\alpha\beta_2$ integrin); MHC II, major histocompatibility complex II; NF- κ B, nuclear factor κ B; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

^aThis drug is under study for sarcoid uveitis.

^bAdalimumab (an anti-TNF antibody) is under investigation for cutaneous sarcoidosis. Atorvastatin and rituximab (anti-CD20 antibodies) are under study for pulmonary sarcoidosis.

^cThis is an important intracellular second messenger, which regulates multiple inflammatory activities including cell trafficking, cell adhesion molecules, cytokines, and microvascular leakage.

regulated by cyclases and the cyclic nucleotide phosphodiesterases, which cleave the 3' 5' cyclic phosphate bonds of these 2 cyclic nucleotides.⁵⁰ Inflammation is suppressed by increased levels of adenosine 3' 5' cyclic monophosphate. Agents that increase adenosine 3' 5' cyclic monophosphate, such as phosphodiesterase inhibitors, might be valuable in inflammatory conditions.⁴⁵ Phosphodiesterase 4 inhibitors may inhibit T-cell activation and numerous T-cell functions mediated via CD28 co-stimulation; methotrexate and cyclosporine may not be as effective in this form of activation. Pentoxifylline (a non-selective phosphodiesterase inhibitor) has known anti-inflammatory properties and has been shown to inhibit TNF.³⁹ An open-label study in Germany reported beneficial effects of pentoxifylline in patients with pulmonary sarcoidosis.⁴⁰ A randomized, double-blind, placebo-controlled trial was conducted at the National Institutes of Health to determine whether pentoxifylline could be an alternative treatment to prednisone. Patients with pulmonary sarcoidosis were given 2000 mg/d of pentoxifylline (in divided doses) as their baseline prednisone dose was tapered or placebo. While the primary analysis showed no difference between the 2 study groups, a post hoc analysis demonstrated fewer flares in the patients who received pentoxifylline compared with those who received placebo. In addition, less prednisone was used in the pentoxifylline group, suggesting a steroid-sparing effect.⁴¹ This study may provide a basis for using more specific, better-tolerated phosphodiesterase inhibitors in future clinical trials.

Statins lower cholesterol levels and have immunomodulatory properties,⁴²⁻⁴⁴ many of which result from inhibition of 3-hydroxy-3-methylglutaryl coenzyme A, which suppresses the synthesis of isoprenoid intermediates of cholesterol biosynthetic pathways. Isoprenoid intermediates are necessary for the posttranslational modification (prenylation) of a variety of proteins, which anchors them to cell

membranes. Interference with protein prenylation can disrupt intracellular targeting of important mediators of inflammation, such as small guanosine triphosphate-binding proteins and the γ subunit of heterotrimeric G proteins.

Statins regulate transcription factors important in inflammation, including NF- κ B, activating protein 1, and peroxisome proliferator-activated receptors, and decrease the expression of co-stimulatory and activation molecules on dendritic cells. They suppress CD4 T_H1 differentiation, limit chemokine production in alveolar macrophages, and disrupt the cell membrane lipid bilayer on T cells, which interferes with activation and signaling. A randomized, double-blind, placebo-controlled trial is under way at the National Institutes of Health to determine if atorvastatin has steroid-sparing effects in adults requiring treatment for pulmonary sarcoidosis (NCT00279708).

CONCLUSION

Sarcoidosis is a multisystem inflammatory disorder of undetermined etiology that has a myriad of manifestations. There are often delays in the diagnosis and care because there is no criterion diagnostic test. Patients are without a treatment approved by the US Food and Drug Administration, consequently glucocorticoids remain the standard of care. Given recent advances in the identification of molecular targets and the emergence of novel therapeutic agents, investigations strategically directed at key immunopathogenic mechanisms should move forward with exigency and resolve.

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Study concept and design: Iannuzzi, Fontana.

Drafting of the manuscript: Iannuzzi, Fontana.

Critical revision of the manuscript for important intellectual content: Fontana.

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