REVIEW ARTICLE

MEDICAL PROGRESS

Sarcoidosis

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THE MODERN HISTORY OF SARCOIDOSIS, AN ENIGMATIC MULTISYSTEM DISEASE, goes back to 1899, when the pioneering Norwegian dermatologist Caesar Boeck coined the term to describe skin nodules characterized by compact, sharply defined foci of "epithelioid cells with large pale nuclei and also a few giant cells."[1] Thinking this resembled sarcoma, he called the condition "multiple benign sarcoid of the skin."[1]

Since sarcoidosis was last reviewed in the *Journal* 10 years ago,[2] more than 5000 articles related to this condition have been published. This review summarizes recent advances and addresses pitfalls in the diagnosis and treatment of sarcoidosis.

EPIDEMIOLOGY

Sarcoidosis affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years.[3] The incidence of sarcoidosis varies widely throughout the world, probably because of differences in environmental exposures, surveillance methods, and predisposing HLA alleles and other genetic factors. The highest annual incidence of sarcoidosis has been observed in northern European countries (5 to 40 cases per 100,000 people).[4] In Japan, the annual incidence ranges from 1 to 2 cases per 100,000 people[4] and peaks in the third decade of life. The adjusted annual incidence among black Americans is roughly three times that among white Americans (35.5 cases per 100,000, as compared with 10.9 per 100,000).[3] In black Americans, the peak incidence occurs later in life — in the fourth decade in both men and women — as compared with other groups.[3] Sarcoidosis is also more likely to be chronic and fatal in black Americans.[5] A preponderance of cases of sarcoidosis in females is consistent across racial and ethnic groups. In Scandinavia, the incidence in women appears to be bimodal, with one peak at 25 to 29 years of age and another at 65 to 69 years of age.[6]

Socioeconomic status does not affect the risk of sarcoidosis, but low income and other financial barriers to care are associated with more severe sarcoidosis at presentation, even with adjustment for the demographic characteristics of race or ethnic group, sex, and age.[7]

SEARCH FOR ENVIRONMENTAL CAUSES

Because sarcoidosis most commonly involves the lungs, eyes, and skin, the search for environmental causes has centered on exposures to airborne antigens. Some of the earliest studies of sarcoidosis reported associations with exposures to irritants found in rural settings, such as emissions from wood-burning stoves and tree pollen.[8] More recently, associations with sarcoidosis and exposure to inorganic particles,[9] insecticides,[10] and moldy environments[10,11] have been reported. Occupational

studies have shown positive associations with service in the U.S. Navy,[12] metalworking,[11] firefighting,[13] and the handling of building supplies.[14] Recently, Izbicki et al. reported an increased incidence of sarcoidosis among New York City Fire Department rescue workers involved in the 2001 World Trade Center disaster.[15]

With the use of polymerase-chain-reaction techniques, mycobacterial and propionibacterial DNA and RNA have been recovered from sarcoidal tissue.[16] Investigators have reported that serum samples from patients with sarcoidosis often contain antibodies to mycobacterial antigens, including recombinant *Mycobacterium tuberculosis* katG,[17] *M. tuberculosis* heat-shock protein 70,[18] and *M. tuberculosis* mycolyl transferase antigen 85A.[19] Given the multiple environmental risk factors reported to date, it seems credible that the development of sarcoidosis is probably the end result of immune responses to various ubiquitous environmental triggers.

GENETIC FEATURES

Familial sarcoidosis was first reported in 1923 in two affected sisters.[20] No formal twin study has been reported, but the concordance appears to be higher in monozygotic twins than in dizygotic twins.[21]

In A Case-Control Etiologic Sarcoidosis Study (ACCESS), patients with sarcoidosis stated five times as often as control subjects that they had siblings or parents with sarcoidosis.[22] Although siblings of patients with sarcoidosis are at increased risk for the disease, the phenotypic features and clinical outcomes in affected sibling pairs exhibit minimal concordance, with the exception that probands with ocular or hepatic involvement are more likely to have siblings with similar manifestations (odds ratio for ocular involvement, 3.0; 95% confidence interval [CI], 1.7 to 5.4; odds ratio for hepatic involvement, 3.3; 95% CI, 1.5 to 7.4).[23]

The first reported association between sarcoidosis and specific gene products was the association between class I HLA-B8 antigens and acute sarcoidosis.[24] Subsequently, HLA class II antigens, encoded by HLA-DRB1 and DQB1 alleles, have been consistently associated with sarcoidosis.[25,26]

The antigen-binding properties of the HLA class II peptide-binding groove are determined by polymorphic amino acid residues. These residues form pockets in the groove, interacting with the antigenic peptide side chains. A recent study suggests that pocket 9 of HLA-DQ and pocket 4 of HLA-DR are the most important regions involved in the association with sarcoidosis.[27] Additional reports suggest that specific HLA genotypes confer a predisposition to the disease phenotype rather than to susceptibility.[26,28] For example, HLA-DQB1*0201 and HLA-DRB1*0301 are strongly associated with acute disease and a good prognosis.[28]

The results of studies of non-HLA candidate genes have been inconsistent.[29] Genes encoding for tumor necrosis factor α (TNF-α), interferon-γ, and chemokine receptors are logical candidates on the basis of their functions, but associations with sarcoidosis have not been confirmed.[30,31]

To date, two genomewide scans for loci associated with sarcoidosis have been reported: one in white Germans,[32] which showed the strongest linkage signals at chromosomes 3p and 6p, and the other in black Americans,[33] which showed the strongest signals at chromosomes 5p and 5q. However, the outcome of genomewide scans is known to be influenced by the population studied.

Valentonyte et al.[34] reported an association of the butyrophilin-like 2 (*BTNL2*) gene on chromosome 6p with sarcoidosis, and others have confirmed this association.[35] *BTNL2*, a B7 family member, probably functions as a negative costimulatory molecule, but how an aberrant function of this gene might result in sarcoidosis is unknown.[36] Subsequent fine-mapping studies in a genomewide sample of black Americans suggest that there are sarcoidosis susceptibility genes on chromosomes 3p and 5q11.2 and protective genes on a region of 5p15.2.[37] Phenotypic analysis of these genomewide scans shows the strongest linkage signals on chromosome 1p36 for radiographic resolution of sarcoidal lesions and on chromosome 18q22 for the presence of cardiac or renal involvement.[38]

Because susceptibility to sarcoidosis depends on both genetic and environmental exposures, identification of interactions between specific sarcoidosis-susceptibility loci and environmental modifiers will probably be important in delineating the cause (or causes) of sarcoidosis.[39] To date, one such interaction has been identified: an association between the HLA-DQB1 sarcoidosis-susceptibility locus and exposure to

water damage or high humidity in the workplace.[26]

IMMUNOPATHOGENESIS

The development and accumulation of granulomas constitute the fundamental abnormality in sarcoidosis (Fig. 1A through 1F). Although the inciting event in sarcoidosis is unknown, in principle, granulomas generally form to confine pathogens, restrict inflammation, and protect surrounding tissue. Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Macrophages, in the face of chronic cytokine stimulation, differentiate into epithelioid cells, gain secretory and bactericidal capability, lose some phagocytic capacity, and fuse to form multinucleated giant cells (Fig. 1D).[40] In more mature granulomas, fibroblasts and collagen encase the ball-like cluster of cells (Fig. 1E), and in some cases, sclerosis ensues, altering organ architecture and function (Fig. 1F).

A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas (Fig. 2).[41] The oligoclonal $\alpha\beta$ T-cell repertoire observed in sarcoidosis suggests that the triggering antigens favor progressive accumulation and activation of selective T-cell clones.[42] These activated CD4+ cells differentiate into type 1 helper T (Th1)–like cells and secrete predominantly interleukin-2 and interferon-γ, augment macrophage TNF-α production, and amplify the local cellular immune response.[43] A subgroup of regulatory T cells, natural killer T cells, has been found to be greatly reduced in peripheral blood from patients with sarcoidosis who do not have Löfgren's syndrome.[44] However, there are conflicting data on the accumulation of natural killer T cells in granulomatous lesions. For example, natural killer T cells were found in lymph-node specimens but not in skin lesions.[45] The role of natural killer T cells in sarcoidosis remains undefined.

Sarcoidosis also presents an "immune paradox": despite extensive local inflammation, anergy may develop, as indicated by suppression of the immune response to tuberculin.[46] Expansion of $CD25^{bright}$ regulatory T cells, a subgroup of CD4+ T lymphocytes, in active sarcoidosis, may account for this anergy[46] by abolishing interleukin-2 production and strongly inhibiting T-cell proliferation.[46]

Sarcoidosis has been reported to develop after interferon alfa therapy for hepatitis C.[47] Some studies have suggested that hepatitis C infection itself may increase the risk of sarcoidosis,[48] but it appears more likely that treatment with interferon alfa increases interferon-γ and interleukin-2, thus promoting granuloma formation.[49]

Although granulomas may resolve with little consequence, pulmonary fibrosis occurs in 20 to 25% of patients with sarcoidosis. The pathogenesis of pulmonary fibrosis in sarcoidosis remains uncertain. Matrix metalloproteinases, particularly matrix metalloproteinases 8 and 9, have been reported to be increased in bronchoalveolar-lavage specimens and sputum from patients with sarcoidosis; at the same time, the bronchial-lavage samples from these patients did not show a compensatory increase in the levels of tissue inhibitor of metalloproteinase 1.[50,51] Thus, unopposed

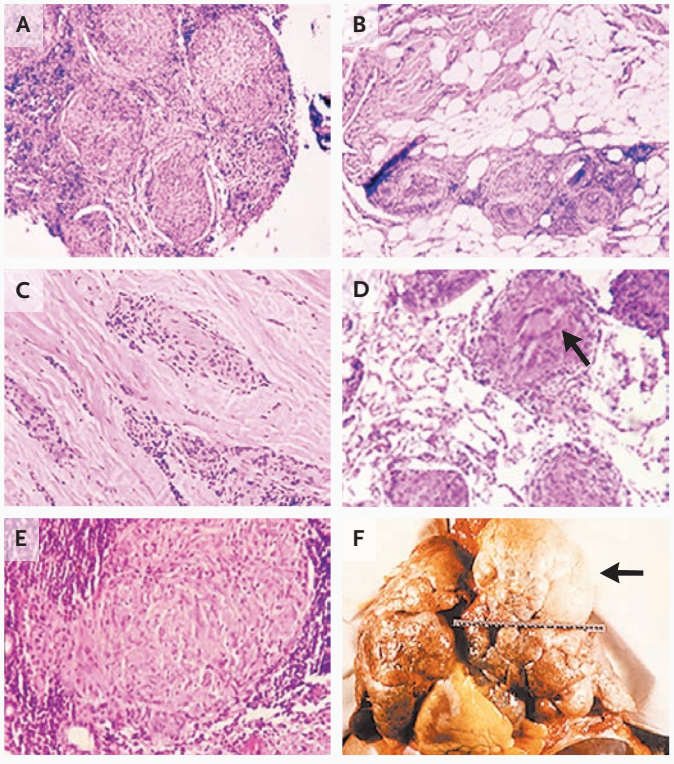

Figure 1. Spectrum of Pathological Findings in Patients with Sarcoidosis.
Granulomas are shown in nasal mucosal tissue (Panel A), synovial tissue (Panel B), a scar on the skin (Panel C), the lung (Panel D, arrow points to giant cell), a lacrimal gland (Panel E), and the heart and lungs at autopsy (Panel F, arrow points to upper-lobe bullae).

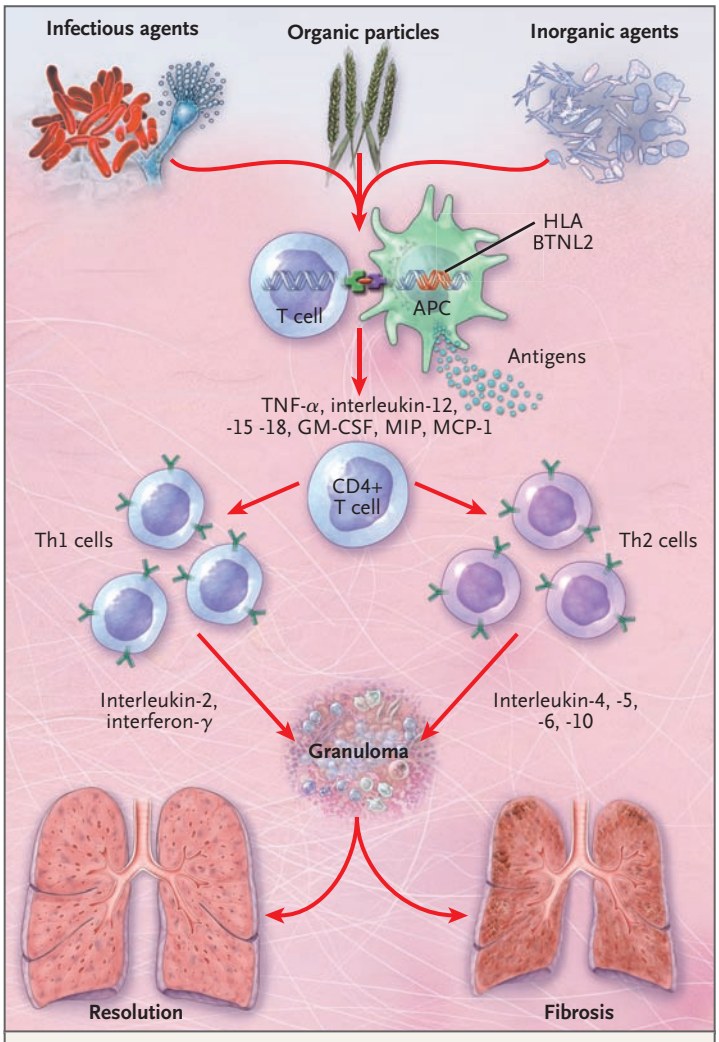

Figure 2. Hypothesized Immunopathogenesis of Sarcoidosis.

Infectious, organic, and inorganic agents are possible antigens in sarcoidosis. Any causative microbe, if present, is probably cleared, leaving behind an undegradable product or initiating a cross-reacting immune response to self-antigen. Antigen-presenting cells (APC), in addition to producing high levels of tumor necrosis factor alpha (TNF-α), secrete interleukin-12, -15, and -18, macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein 1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF).[41] A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with APCs to initiate the formation and maintenance of granulomas. CD4+ T cells release interleukin-2 and interferon-γ. Activated CD4+ cells differentiate into type 1 helper (Th1)-like cells and secrete predominantly interleukin-2 and interferon-γ. The efficiency of antigen processing, antigen presentation, and cytokine release is probably under genetic control; evidence strongly supports a role for macrophage HLA and BTNL2 alleles in sarcoidosis susceptibility and phenotype.[34,35] However, T-cell genes that may confer a predisposition to sarcoidosis or affect the phenotype have not yet been identified. Sarcoidal granulomas are organized, structured masses composed of macrophages and their derivatives, epithelioid cells, giant cells, and T cells. Sarcoidal granulomas may persist, resolve, or lead to fibrosis. Alveolar macrophages activated in the context of a predominant type 2 helper (Th2) T-cell response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis.

protease activity initiates extracellular-matrix breakdown and remodeling. A shift from cytokines produced by Th1 cells (mainly interleukin-2 and interferon-γ) to cytokines produced by type 2 helper T (Th2) cells (mainly interleukins 4, 10, and 13) also appears to be central to the development of fibrosis.[52] Alveolar macrophages activated in the context of Th2 cytokines produce high levels of fibronectin and the CC motif ligand 18 (CCL18) chemokine.[53] CCL18 up-regulates collagen production by lung fibroblasts, which in turn increases macrophage release of CCL18, creating a positive feedback loop leading to pulmonary fibrosis.[53]

CLINICAL FEATURES

Principles for managing the care of patients with sarcoidosis are listed in Table 1; common clinical features are shown in Figure 3. Sarcoidosis often first comes to attention when abnormalities are detected on a chest radiograph during a routine screening examination. Systemic symptoms such as fatigue, night sweats, and weight loss are common; the organ system that is most affected varies with the given patient. Löfgren's syndrome, an acute presentation consisting of arthritis, erythema nodosum, and bilateral hilar adenopathy, occurs in 9 to 34% of patients.[54] This acute variant of the disease presents differently in men and women.[55] Erythema nodosum is observed predominantly in women, and marked ankle periarticular inflammation or arthritis without erythema nodosum is more common in men.[56]

Two thirds of patients with sarcoidosis generally have a remission within a decade after diagnosis, with few or no consequences; remission occurs for more than half of patients within 3 years. Unfortunately, up to a third of patients have unrelenting disease, leading to clinically significant organ impairment. A recurrence after 1 or more years of remission is uncommon (affecting <5% of patients), but recurrent disease may develop at any age and in any organ. Less than 5% of patients die from sarcoidosis; death is usually the result of pulmonary fibrosis with respiratory failure or of cardiac or neurologic involvement.

DIAGNOSIS

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic find-

ings, supported by histologic evidence in one or more organs of noncaseating epithelioid-cell granulomas in the absence of organisms or particles. A diagnosis of sarcoidosis is reasonably certain without biopsy in patients who present with Löfgren's syndrome. In all other cases, a biopsy specimen should be obtained from the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If diagnosis requires pulmonary tissue, transbronchial biopsy by means of bronchoscopy has a diagnostic yield of at least 85% when multiple lung segments are sampled.

Sarcoidal granulomas have no unique histologic features to differentiate them from other granulomas. Special stains for acid-fast bacilli and fungi, as well as cultures of such organisms, are essential. If the results of lung biopsy with bronchoscopy are negative and other organs are not obviously involved, biopsy of intrathoracic lymph nodes, which are often enlarged in patients with sarcoidosis, may be necessary to confirm the diagnosis. Endoscopic ultrasound-guided, fine-needle aspiration of intrathoracic lymph nodes has been reported to provide a diagnostic yield of approximately 82% and may obviate the need for mediastinoscopy.[57]

The Kveim–Siltzbach test has been used for many years in the diagnosis of sarcoidosis. The test is performed by injecting homogenate of human sarcoid tissue extract intradermally; 4 weeks later, the papule that develops at the site of injection is biopsied. This test is now used less often for several reasons. First, no commercially available preparation of the antigen exists. Second, the use of human tissue extracts for clinical purposes presents many constraints. Third, each new Kveim–Siltzbach preparation requires validation in vivo. Kveim–Siltzbach testing, if available, is most useful in patients whose lesions are not easily accessible by biopsy (i.e., lesions at sites other than the skin, lacrimal glands, peripheral lymph nodes, and conjunctivae) and who do not need immunosuppressive treatment during the

Table 1. Diagnosis, Clinical Characteristics, and Treatment of Sarcoidosis.*

Diagnosis
Diagnosis of sarcoidosis is firm when chest radiographic evidence is accompanied by compatible clinical features and noncaseating granulomas on biopsy, with all other causes of granulomas ruled out.
Biopsy is indicated for all patients presumed to have sarcoidosis, except those with Löfgren's syndrome.
Pathologists can identify granulomas, but the diagnosis should not be based on pathological findings alone.
A response to corticosteroid therapy does not establish the diagnosis of sarcoidosis.
Measurement of the serum angiotensin-converting–enzyme level is an insensitive and nonspecific diagnostic test and a poor therapeutic guide.
For patients without apparent lung involvement, ^{18}FDG PET is useful in identifying sites for diagnostic biopsy.
^{18}FDG PET and MRI with gadolinium detect cardiac and neurologic involvement. (Caution in the use of gadolinium is needed, given the possibility that nephrogenic fibrosing sclerosis may develop in patients with chronic kidney disease.)
CT imaging is unnecessary for most patients with sarcoidosis. CT is indicated when the chest radiograph is atypical for sarcoidosis or when hemoptysis occurs.
Clinical characteristics
Constitutional symptoms such as fatigue may predominate.
Cardiac sarcoidosis is much more common than reported previously and may cause loss of ventricular function and sudden death.
Cardiac and neurologic sarcoidosis may occur without apparent disease activity in other organs.
Chest radiographic patterns (stages 1, 2, and 3) do not reflect the chronology of the disease.
Treatment
Most patients with sarcoidosis do not require therapy.
There have been few well-controlled studies of the use of any therapeutic agent in patients with sarcoidosis — be skeptical of anecdotal reports.
Treatment for pulmonary sarcoidosis is best guided by pulmonary-function studies.
Deforming sarcoidal skin lesions are usually chronic and require prolonged therapy.

* ^{18}FDG PET denotes ^{18}F-fluorodeoxyglucose positron-emission tomography, MRI magnetic resonance imaging, and CT computed tomography.

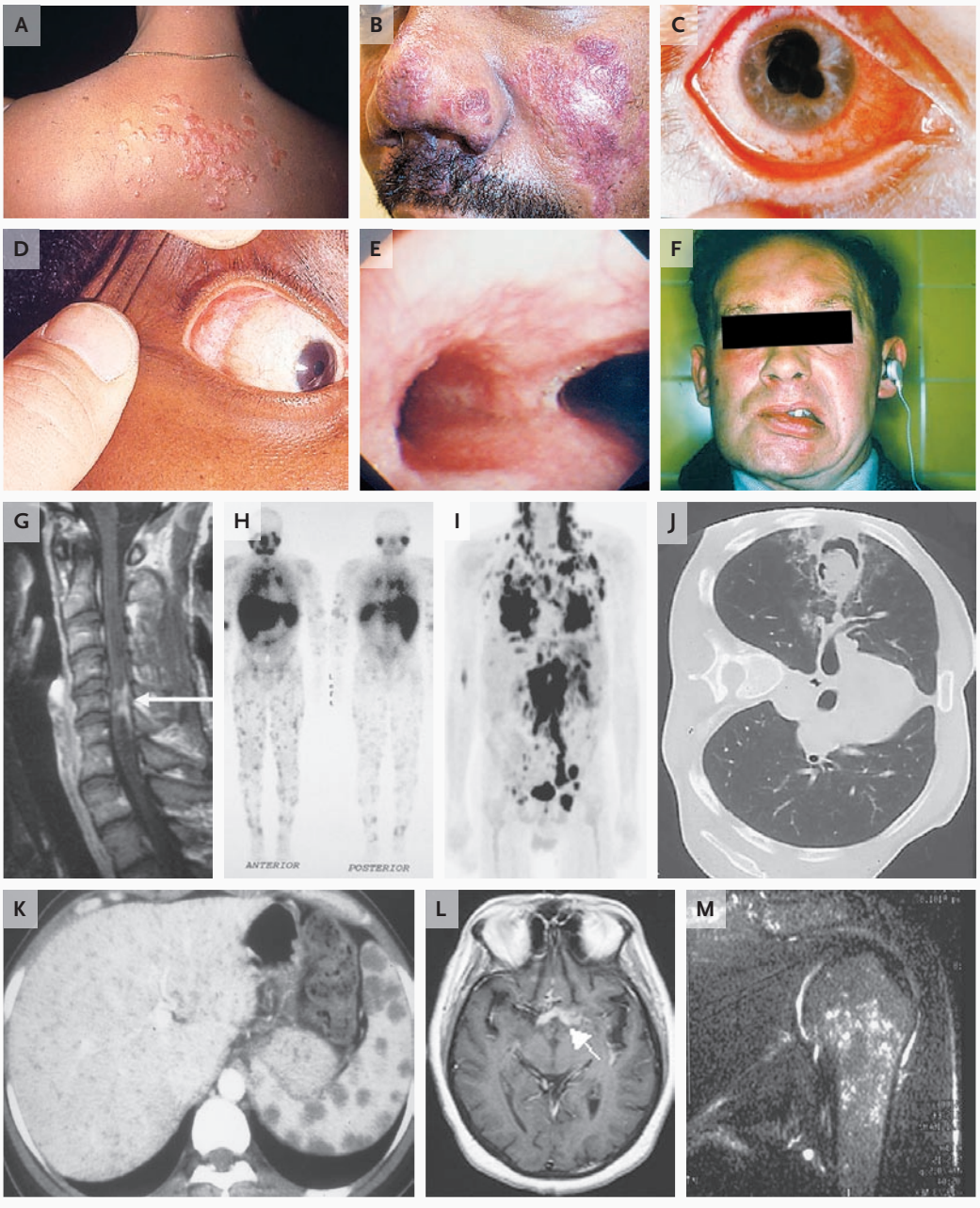

Figure 3. Clinical Features of Sarcoidosis.

Panel A shows waxy interscapular skin plaques; Panel B, lupus pernio (violaceous plaques on the cheek and nose); Panel C, anterior uveitis with synechiae; Panel D, an enlarged, nodular lacrimal gland; Panel E, endobronchial cobblestoning; Panel F, ipsilateral peripheral facial-nerve and cranial-nerve involvement with hearing loss; Panel G, a spinal cord mass on a T_1-weighted MRI scan (arrow); Panel H, nasal, parotid, lung, liver, spleen, subcutaneous-nodule, and mediastinal and epitrochlear lymph-node involvement on a gallium scan; Panel I, hypermetabolism in the liver, spleen, and lymph nodes on a positron-emission tomographic scan with ^{18}F-fluorodeoxyglucose; Panel J, a right-lung cavity with a gravity-dependent aspergilloma; Panel K, hypodense nodular splenic masses on an abdominal computed tomographic scan; Panel L, involvement of the optic chiasm on a gadolinium-enhanced MRI scan (arrow); and Panel M, granulomatous involvement of the humerus on a T_1-weighted MRI scan.

4-week waiting period between injection and biopsy. On the basis of our experience over the past 50 years at Mt. Sinai Medical Center, New York, where more than 10,000 Kveim–Siltzbach tests have been performed, the rate of true positive results appears to be over 50%, and the rate of false positive results is close to zero. A 3-to-4-mm scar from the punch biopsy necessitated by the test has been the only complication.

Without a definitive diagnostic imaging study, fluid analysis, or blood test, sarcoidosis remains a diagnosis of exclusion. Guidelines for initial clinical evaluation and follow-up are provided in Table 2.[58,59] Recently, several reports suggested that ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}FDG PET) may be useful in assessing the extent of organ involvement and in pinpointing the organs that are candidates for diagnostic biopsy.[60]

Sarcoidal granulomas produce angiotensin-converting enzyme (ACE), and ACE levels are elevated in 60% of patients with sarcoidosis. However, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. Although ACE levels are influenced by ACE gene polymorphisms, and genotype-corrected reference values may be used to improve interpretation,[61] as a diagnostic tool, measurement of serum ACE levels lacks sensitivity and specificity. For example, the positive and negative predictive values were only 84% and 74%, respectively, in one series.[62]

ORGAN INVOLVEMENT

Sarcoidal granulomas can involve any organ, but in more than 90% of patients, clinical sarcoidosis is manifested as intrathoracic lymph-node enlargement, pulmonary involvement, skin or ocular signs and symptoms, or some combination of these findings.

PULMONARY INVOLVEMENT

Respiratory symptoms often include dyspnea, cough, vague chest discomfort, and wheezing. Chest radiographs in patients with sarcoidosis have been classified into four stages[63]: stage 1, bilateral hilar lymphadenopathy without infiltration; stage 2, bilateral hilar lymphadenopathy with infiltration; stage 3, infiltration alone; and stage 4, fibrotic bands, bullae, hilar retraction, bronchiectasis, and diaphragmatic tenting. These so-called stages represent radiographic patterns and do not indicate disease chronicity or correlate with changes in pulmonary function.[64]

About 65% of patients have airflow limitation at presentation, and spirometry usually indicates restrictive ventilatory dysfunction, with reduced forced vital capacity (FVC) and reduced forced expiratory volume in 1 second (FEV_1). At least 50% of patients also have concurrent obstructive airway disease, with a reduced ratio of FEV_1 to FVC.[5] Airway hyperreactivity occurs in 5 to 83% of patients.[65] In 80% of patients presenting with abnormal spirometric findings, the values return to the normal range within 2 years.[64]

Pulmonary hypertension is a well-described complication of sarcoidosis. Studies have shown that pulmonary-artery pressure is elevated in 6 to 23% of patients at rest and in as many as 43% with exertion.[66] Fibrosis — and the resulting obliteration of the pulmonary vessels — is the most common mechanism for pulmonary hypertension in sarcoidosis, although granulomatous infiltration of the pulmonary arterioles can cause pulmonary hypertension in the absence of pulmonary fibrosis.[67] The prognosis for patients with sarcoidosis-associated pulmonary hypertension is not known. Several small case series indicate a benefit with a treatment approach similar to that used for primary pulmonary hypertension.[66]

CUTANEOUS INVOLVEMENT

Although not life-threatening, the unsightly skin lesions of sarcoidosis can be emotionally devastating. Skin involvement is common (occurring in 25 to 35% of patients with sarcoidosis) and often overlooked or misinterpreted, given the variability of the lesions. Macules, papules, and plaques may arise as single isolated lesions or in crops. Lesions commonly involve the nape of the neck and upper back (Fig. 3A), extremities, and trunk, and may appear in scars and tattoos. In black American patients, skin lesions frequently leave scars, pits, and pale, depigmented areas.

Lupus pernio (Fig. 3B), the term for sarcoidosis-related indurated, lumpy, violaceous lesions on the nose, cheeks, lips, and ears, can be disfiguring, eroding into underlying cartilage and bone. Lupus pernio is more common in women than in men and is associated with chronic disease and extrapulmonary involvement.[68]

Erythema nodosum occurs in about 10% of patients with sarcoidosis and usually lasts for about 3 weeks. Biopsy specimens of erythema

Table 2. Clinical Evaluation in Sarcoidosis.*

Initial assessment
History and physical examination (attention to environmental or occupational exposure and family history)
Biopsy of affected organ, with special stains and culture of specimen
Posteroanterior and lateral chest radiographs
Pulmonary-function tests — spirometry with bronchodilator, total lung capacity, and diffusion capacity
Electrocardiography
Complete ophthalmologic evaluation (slit-lamp, tonometric, and funduscopic examinations)
Complete blood count with platelet count and measurement of serum calcium, creatine, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels)
Measurement of serum level of angiotensin-converting enzyme (if elevated, may be useful to monitor patient compliance)
Other tests as indicated for assessment of involved organs:
Heart — Holter monitoring, echocardiography, cardiac PET, MRI, and electrophysiological study for inducible arrhythmias
Lung — right-heart catheterization for pulmonary hypertension
Central nervous system — MRI with gadolinium and cerebrospinal fluid analysis
Monitoring (follow up every 2 to 3 months)
Assessment for decline in physiological function based on initial organ involvement
Further testing in the case of new symptoms or physical findings
Testing to monitor side effects of therapy — for example, bone densitometry for corticosteroid use and semiannual ophthalmologic examination for hydroxychloroquine use

* PET denotes positron-emission tomography.

nodosum lesions show nonspecific septal panniculitis, which neither confirms nor negates the diagnosis of sarcoidosis.

LIVER AND SPLEEN INVOLVEMENT

Just over 10% of all patients with sarcoidosis have elevated serum aminotransferase and alkaline phosphatase levels.[5] A cholestatic syndrome characterized by pruritus and jaundice, hepatic failure, or portal hypertension can develop; yet liver involvement is usually clinically silent. Detection of hepatic and splenic lesions on computed tomography is described in 5% and 15% of patients, respectively (Fig. 3K).[69] Nearly 60% of patients with hepatic manifestations of sarcoidosis have constitutional symptoms such as fever, night sweats, anorexia, and weight loss. Liver involvement is at least twice as common in black Americans as in white Americans.[70] Portal hypertension with variceal bleeding, a hepatopulmonary syndrome with refractory hypoxemia, and cirrhosis leading to liver failure occur in only 1% of patients with sarcoidosis.[71]

NEUROLOGIC INVOLVEMENT

The central nervous system is involved in up to 25% of patients with sarcoidosis who undergo autopsy, but only 10% of all patients with sarcoidosis present with neurologic symptoms. The most common problems, listed in decreasing order of frequency, are cranial-nerve palsies, headache, ataxia, cognitive dysfunction, weakness, and seizures.[72] Neurologic involvement precedes the diagnosis of sarcoidosis in up to 74% of patients and is the only manifestation in 10 to 17% of patients with neurosarcoidosis.[73]

Analysis of cerebrospinal fluid in patients with central nervous system involvement indicates nonspecific lymphocytic inflammation. The diagnostic value of measuring ACE levels in cerebrospinal fluid is controversial, since ACE levels are neither sensitive nor specific for the diagnosis.[74] In a third of patients, oligoclonal immunoglobulin bands in the cerebrospinal fluid are elevated, making it difficult to differentiate sarcoidosis from multiple sclerosis.[74]

Magnetic resonance imaging (MRI) with gadolinium is useful for detecting central nervous system involvement and guiding therapy. An aggressive approach to treatment, with the use of both corticosteroids and immunosuppressive agents such as azathioprine, has recently been advocated.[72] Treatment of lesions that are evident on MRI should be continued until sustained resolution occurs, as assessed by means of the same imaging technique.

OPHTHALMOLOGIC COMPLICATIONS

The eye and adnexa (Fig. 3C) are involved in 25 to 80% of patients with sarcoidosis, necessitating routine slit-lamp and funduscopic examination.[75] Anterior uveitis is the most common manifestation, occurring in 65% of patients with ophthalmologic involvement; chronic anterior uveitis, with insidious symptoms leading to glaucoma and vision loss, is more common than acute anterior uveitis. Posterior-segment involvement is reported to occur in nearly 30% of the patients with ocular sarcoidosis and is frequently accompanied by central nervous system involvement.[75] In about 10 to 15% of patients with uveitis, both the anterior and posterior segments are involved.

CARDIAC SARCOIDOSIS

Cardiac granulomas are found in about 25% of patients with sarcoidosis who are examined at autopsy, but cardiac sarcoidosis is clinically apparent in only about 5% of all patients. The most common location for granulomas and scars is the left ventricular free wall, followed by the intraventricular septum, often with involvement of the conducting system. Cardiac sarcoidosis is manifested clinically as a cardiomyopathy with loss of muscle function or tachyarrhythmias and bradyarrhythmias (palpitations, syncope, and death). Endomyocardial biopsy has a low diagnostic yield (less than 20%) because cardiac involvement tends to be patchy, and granulomas are more likely to be located in the left ventricle and basal ventricular septum than in the right ventricle, where endomyocardial biopsies are usually performed.[76] Cardiac MRI with gadolinium enhancement and PET scanning are valuable aids in the diagnosis of myocardial sarcoidosis. Since sudden death may be the first sign of cardiac sarcoidosis, electrophysiological studies to detect any conduction delays or increased risk of sustained arrhythmias should be strongly considered in all patients with suspected cardiac sarcoidosis. Most authorities recommend placement of an electronic pacemaker for complete heart block and an automatic implantable cardioverter–defibrillator for ventricular fibrillation or tachycardia and markedly reduced left ventricular ejection fraction.[77]

HYPERCALCEMIA AND RENAL DISEASE

Hypercalciuria occurs in 40% of patients with sarcoidosis, hypercalcemia in 11%, and renal calculi in 10%. Therefore, 24-hour urinary excretion of calcium should be measured in all patients with sarcoidosis.[78] Intrarenal calcium deposition may be so severe that renal failure ensues. Calcium metabolism is disturbed because sarcoidal macrophages possess 25-hydroxyvitamin D–1α-hydroxylase, which converts 25-hydroxyvitamin D to the more active vitamin D metabolite, 1,25 dihydroxyvitamin D. Renal failure due to granulomatous nephritis rarely occurs.

BONE AND JOINT INVOLVEMENT

With new imaging techniques (MRI and PET), bony lesions scattered throughout the skeleton are often detected in patients with sarcoidosis and may be confused with metastatic bone lesions. Although skeletal lesions may cause pain, most are asymptomatic. Chronic arthralgias are more common than frank arthritis.

SARCOIDOSIS IN CHILDREN

Sarcoidosis is less common in children than in adults. In a 15-year study in Denmark,[79] the incidence of sarcoidosis was 0.06 case per 100,000 children 4 years of age or younger, increasing gradually with age to 1.02 cases per 100,000 children who were 14 to 15 years old. In older children, the clinical picture was similar to that in adults. Younger children presented predominantly with skin lesions, uveitis, arthritis, and stage 1 changes on chest radiographs. Familial juvenile systemic granulomatosis, also called Blau's syndrome, bears some similarities to childhood sarcoidosis.[80] Children with Blau's syndrome also present with granulomatous arthritis and skin and eye involvement. However, in Blau's syndrome, the lungs are not involved, the Kveim–Siltzbach skin test is negative, and the Blau genetic mutation (which involves the CARD15 protein) is not associated with sarcoidosis.[29,81]

THERAPY

MEDICATIONS

Most patients with sarcoidosis are not disabled by the illness, so the decision to provide treatment should reflect a weighing of the risks of using corticosteroids, the most common therapy, against the potential benefits. A general rule is to consider instituting treatment when organ function is threatened. Detection of granulomatous disease on physical examination, biopsy, imaging

studies, or serologic testing is not a mandate to provide treatment. Table 3 presents treatment guidelines. An international expert panel has suggested initiating treatment with oral prednisone at a dose of 20 to 40 mg per day.[59] The panel recommends evaluating the response to treatment after 1 to 3 months. If there has been a response, the prednisone dose should be tapered to 5 to 15 mg per day, with treatment planned for an additional 9 to 12 months. Lack of a response after 3 months suggests the presence of irreversible fibrotic disease, nonadherence to therapy, or an inadequate dose of prednisone. Once treatment with prednisone has been initiated, limiting it to short courses is unlikely to be helpful.

Most published data on the use of immunosuppressive and cytotoxic drugs in patients with sarcoidosis are anecdotal and based on small numbers of patients.[82] The only randomized, controlled trial that has been reported to date compared methotrexate with placebo in patients receiving corticosteroids.[83] After 12 months, those receiving methotrexate required significantly smaller amounts of corticosteroids than the control group. No significant differences were found between the methotrexate and control groups in terms of lung function, chest radiographs, symptoms, or side effects.

Hydroxychloroquine has been used with some success, particularly for hypercalcemia,[84] skin disease, and neurologic involvement.[85] Bachelez et al. reported on the use of minocycline in 12 patients; the drug was effective for the treatment of skin lesions in 10 patients and diminished lung disease in 2.[86] Several mechanisms have been proposed supporting the use of tetracyclines and their analogues in sarcoidosis. These drugs inhibit matrix metalloproteinases, angiogenesis, apoptosis, and in vitro granuloma formation by monocytes exposed to dextran beads.[87]

Since TNF-α plays a central role in granulo-

Table 3. Initial Therapy According to Organ and Clinical Status.*

Organ	Clinical Findings	Treatment
Lungs	Dyspnea plus FEV_1, FVC <70%	Prednisone, 20–40 mg/day
	Cough, wheezing	Inhaled corticosteroid
Eyes	Anterior uveitis	Topical corticosteroid
	Posterior uveitis	Prednisone, 20–40 mg/day
	Optic neuritis	Prednisone, 20–40 mg/day
Skin	Lupus pernio	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day Thalidomide, 100–150 mg/day Methotrexate, 10–15 mg/wk
	Plaques, nodules	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day
	Erythema nodosum	NSAID
Central nervous system	Cranial-nerve palsies	Prednisone, 20–40 mg/day
	Intracerebral involvement	Prednisone, 40 mg per day Azathioprine, 150 mg/day Hydroxychloroquine, 400 mg/day
Heart	Complete heart block	Pacemaker†
	Ventricular fibrillation, tachycardia	AICD
	Decreased LVEF (<35%)	AICD; prednisone, 30–40 mg/day
Liver	Cholestatic hepatitis with constitutional symptoms	Prednisone, 20–40 mg/day Ursodiol, 15 mg/kg of body weight per day
Joints and muscles	Arthralgias	NSAID
	Granulomatous arthritis	Prednisone, 20–40 mg/day
	Myositis, myopathy	Prednisone, 20–40 mg/day
Hypercalciuria and hypercalcemia	Kidney stones, fatigue	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day

* FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, LVEF left ventricular ejection fraction, AICD automatic implantable cardiac defibrillator, and NSAID nonsteroidal antiinflammatory drug.
† Most authorities recommend a dual-chamber pacemaker–defibrillator.

ma formation, agents that inhibit TNF-α would appear to be potentially useful in treating sarcoidosis.[88] Both thalidomide and pentoxifylline suppress TNF-α production, but neither has been well studied in sarcoidosis. Several case reports, a few case series, and one randomized, controlled trial involving the use of the TNF-α blockers infliximab and etanercept to treat chronic or refractory sarcoidosis have been published.[89,90] Although the case reports and case series were encouraging, the results of the randomized, controlled trial,[90] 6 months in length, indicated only modest improvement in FVC and chest radiographic findings and no differences in dyspnea scores or 6-minute walking distance.

TRANSPLANTATION

About 3% of lung transplantations and less than 1% of heart and liver transplantations are performed in patients with sarcoidosis.[91] The 1- and 5-year graft survival rates for lung and liver transplants in patients with sarcoidosis are similar to those for lung and liver transplants in patients with other disorders. On the basis of data from the United Network for Organ Sharing on orthotopic heart transplantations performed between 1987 and 2005, the 65 patients with sarcoidosis who received transplants had higher rates of short- and intermediate-term survival than the majority of the other recipients.[92] An elevated right atrial pressure (>15 mm Hg) is a marker of increased mortality among patients awaiting lung transplantation; such patients have a 5.2-fold increase in the risk of death.[93,94] Sarcoidosis can recur in lung allografts, but such recurrence does not affect survival or the risk of complications.

FUTURE DIRECTIONS

Despite much research over the past decade, the cause of sarcoidosis remains unknown. A working group convened by the National Heart, Lung, and Blood Institute proposed a number of research directions[95] that included performing mechanistic studies to elucidate granuloma formation; identifying unique proteins, particularly in the Kveim reagent, that may be serving as antigens in sarcoidosis; searching for candidate genes based on the results of published genomewide scans; developing relevant animal models; and performing randomized, controlled trials to test new therapies. Given the new technologies available, research over the next decade may improve our understanding of sarcoidosis and lead to more specific therapies.

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