

Sarcoidosis: Current Concepts And Case Reports

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Abstract: Sarcoidosis is a systemic granulomatous disease of unknown etiology associated with various immune alterations and biochemical changes. This article reports recent advances in the conceptualization of the immune dysfunction with emphasis on helper T-cell overactivity in the lungs. Because 90 percent of patients with sarcoidosis have intrathoracic disease, the mode of presentation, ra-

diographic findings, clinical course, and treatment of pulmonary involvement are discussed. Case reports are used to demonstrate the typical course of the disease and generally favorable outcome of the vast majority of patients seen in the non-referral setting. A rare case of neurosarcoidosis with neuroendocrine features is presented. (J Am Bd Fam Pract 1988; 1:211-7.)

Sarcoidosis is a multisystem granulomatous disease of unknown etiology most commonly affecting young adults and is associated with various immune alterations. Almost any organ or tissue may be involved, although there is a marked predilection for the lungs and adjacent lymph nodes.

Histologically, it is characterized by the presence of noncaseating granulomas, collections of epithelioid and giant cells surrounded by a peripheral rim of lymphocytes having the capability of potent enzyme secretion. Because granuloma formation occurs in many unrelated conditions such as histoplasmosis, tuberculosis, brucellosis, regional enteritis, and berylliosis, the diagnosis of sarcoidosis depends on the exclusion of other diseases and the presence of clinical findings compatible with the known morphologic features of sarcoidosis.¹ In addition, the identification of various immunologic alterations and biochemical markers provides supporting evidence for the diagnosis of active disease.

Laboratory Findings

In 1975, the level of serum angiotensin-converting enzyme (SACE) was shown to be elevated in the majority of patients with active sarcoidosis.² This enzyme is normally found in the endothelial cells of pulmonary capillaries but appears to be abnormally produced by some cellular element in the sarcoid granuloma. Elevated SACE levels are

also present in nonsarcoid disorders such as Gaucher's disease, leprosy, histoplasmosis, diabetes mellitus, and hyperthyroidism. Fortunately, SACE is rarely elevated in tuberculosis, other interstitial pulmonary diseases, lung cancer, or lymphoma. Therefore, with some reservations, a high SACE level is indicative of sarcoidosis, although a normal level does not exclude the diagnosis. Elevated levels are more likely to occur with chronic active disease, and declining levels generally parallel clinical improvement.³

Recent studies based upon bronchoalveolar lavage (BAL) and lung biopsy specimens have demonstrated considerable T-cell accumulation in areas characterized by granuloma formation in contrast to peripheral lymphopenia and deficit in helper T cells seen in patients with active disease. This explains the depression of delayed hypersensitivity and the frequent finding of skin test anergy and a shift from positive to depressed tuberculin reactivity. The heightened immune response with excess helper T-lymphocyte activity within the lung has been associated with the secretion of a variety of lymphokines that may be responsible for the progression of alveolitis to granuloma formation, as well as the stimulation of B-lymphocytes to produce immunoglobulins.^{4,5} The imbalance and altered distribution of T cells appear to play a pivotal role in the pathogenesis of sarcoidosis. Unfortunately, because peripheral T-cell dysfunction does not correlate with clinical manifestations or outcome, measurement of the T-cell fraction generally is unsuitable for clinical use. In contrast, because sarcoid patients with alveolitis have increased T-helper cells, BAL has been used in research centers as a technique to

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determine lung activity and to provide a guide for following the course of disease and response to therapy.

Other biochemical findings such as hypergammaglobulinemia and elevated serum lysozyme levels (produced from monocytes and macrophages) are not specific enough to be clinically useful.

The Kveim-Siltzbach test consists of the intradermal inoculation of an antigen composed of human sarcoidal tissue, which on biopsy in 4 to 6 weeks reveals noncaseating granulomas. The test, however, is limited by the lack of availability of standardized antigen, the occurrence of both false-positive and false-negative reactions, and the delay of 4 to 6 weeks for proper interpretation.

Gallium-67 scanning is a noninvasive technique that has been used to identify active sarcoid disease, particularly in the lung where its accumulation appears to reflect the number and activity of pulmonary macrophages. It may be of value in monitoring progress of the disease.⁶

Clinical Manifestations

The clinical manifestations of sarcoidosis are protean, although 90 percent of patients have some evidence of intrathoracic involvement. Many patients are asymptomatic and are identified only by an abnormal chest radiograph. Some will complain of mild shortness of breath and cough, while a smaller number will develop severe dyspnea and progress to pulmonary hypertension, cor pulmonale, and respiratory failure. Pulmonary function testing frequently reveals a restrictive-type pattern. A reduction in compliance and diffusion capacity may be demonstrated, but there is little correlation with the degree of impairment and the appearance of the chest radiograph.

Table 1. *Intrathoracic Sarcoidosis.*

Stage	Findings	Percent of Patients
0	Normal chest radiograph	10
1	Bilateral hilar adenopathy	40
2	Bilateral hilar adenopathy and pulmonary infiltrate	40
3	Extensive pulmonary infiltrate without hilar adenopathy	10

Table 2. *Relative Frequency of Organ Involvement in Sarcoidosis.*

Frequent	Occasional	Uncommon
Lung	Spleen	Bone
Skin	Liver	Heart
Eye	Nervous system	Kidney
Lymph nodes	Parotid gland	

By international agreement, pulmonary involvement is graded into four stages (Table 1).⁵ Hilar and mediastinal lymphadenopathy are extremely common and practically always bilateral. Pleural effusion is identified in up to 10 percent of cases with associated adenopathy or parenchymal changes, but its presence alone should suggest another diagnosis.⁷ Other common manifestations include hepatosplenomegaly (20 percent of patients), ocular involvement (uveitis most frequent), and cutaneous changes including erythema nodosum and lupus pernio. Myocardial involvement can produce arrhythmias and congestive heart failure due to cardiomyopathy. Areas of bone destruction may be identified in the hands on plain radiograph, and muscular weakness of the extremities may be profound. Neurosarcoidosis generally has facial nerve involvement, although hypothalamic (diabetes insipidus) and parenchymal brain involvement can occur. Parotid gland enlargement in association with fever and uveitis (Heerfordt's syndrome) is considered pathognomonic of sarcoidosis. Kidney involvement has been described and is related to hypercalcemia and nephrocalcinosis, glomerulonephritis, or direct granulomatous changes.⁸ The relative frequency of organ involvement is shown in Table 2.

Further elaboration of these clinical manifestations is presented in the following cases, which have been selected from the author's own experience with patients.

Case One—Uveitis and Stage 2 Pulmonary Disease

A 54-year-old black woman sought care for painful red eyes, blurred vision, and photophobia. Bilateral iritis was diagnosed, and she was treated with homatropine and topical prednisone. A chest radiograph revealed bilateral hilar adenopathy

and ill-defined interstitial lung infiltrates. Her SACE level was 29.3 U/dL (normal, less than 30 U/dL), and pulmonary testing revealed moderate restrictive changes even though she had no obvious pulmonary complaints.

Over the ensuing 4 months, the patient developed fatigue, progressive shortness of breath, and worsening eye symptoms. Except for circumcorneal injection, she had no obvious findings. Her SACE rose to 43.5 U/dL, and she was treated with prednisone orally for 1 year, with prompt amelioration of her pulmonary and eye symptoms.

Three months after cessation of prednisone, her uveitis and dyspnea worsened, confirmed by deterioration in pulmonary testing and an elevation of SACE to 51.9 U/dL. Oral prednisone was started again, with prompt improvement in her symptoms, and a tapering dose continued at 5–10 mg daily for the next 2 years.

At present, except for anterior synechiae in her eyes, she remains asymptomatic despite the fact she is not taking prednisone. Her chest radiograph shows stable lesions, and her current SACE is 10.1 U/dL.

Discussion

Anterior uveitis may be the presenting manifestation of sarcoidosis and may cause severe visual impairment, cataract formation, and secondary glaucoma. All patients with sarcoidosis should undergo careful slit-lamp evaluation. Other eye findings include choreoretinitis, conjunctivitis, lacrimal gland involvement, and, rarely, papilledema. Chronic uveitis is associated with a progressive indolent course in most patients.⁸ Elevated SACE levels can predict relapse such as this patient experienced. Oral prednisone was indicated because of her progressive dyspnea and worsening uveitis, which occurred despite topical steroids.

Case Two—Night Sweats and Abnormal Chest Radiograph

A 31-year-old white man had a 3-month history of night sweats without weight loss or pulmonary symptoms. His physical examination was unremarkable, but the chest radiograph showed right paratracheal lymphadenopathy. His SACE level was 16.8 U/dL, and skin tests showed anergy to PPD and tetanus toxoid antigens.

Mediastinoscopy identified large lymph nodes, which were completely replaced by non-caseating granulomas. Multinucleated giant cells were abundant, and some contained asteroid bodies. Special stains for TB and fungi were negative. The patient did not receive any specific therapy, and his symptoms subsided after 2 months. At a follow-up examination 1 year later, he remained asymptomatic, and his SACE level was 5.9 U/dL.

Discussion

Unilateral hilar adenopathy is unusual in sarcoidosis and requires exclusion of other diseases. Much more common is the radiographic presentation of bilateral hilar adenopathy associated with right paratracheal adenopathy. Fever, weight loss, and fatigue are common but nonspecific constitutional symptoms. Persistent fever requires particular exclusion of tuberculosis and malignancy. Stage 1 pulmonary disease does not require specific treatment unless pulmonary function is severely impaired.⁵ Spontaneous remission and clearing of hilar adenopathy occur in 60 percent of patients. The SACE level may be normal in up to one-third of proven sarcoidosis patients.

Case Three—Erythema Nodosum and Hilar Adenopathy

A 33-year-old white woman experienced acute polyarthralgia, swollen ankles, and tender red nodules bilaterally along the pretibial skin. Chest radiograph revealed a left hilar mass. Mediastinal exploration identified lymphadenopathy, which on biopsy showed almost total ablation by non-caseating granulomas. Special stains for acid-fast bacillus and fungi were negative.

She was treated with aspirin, and her symptoms gradually diminished over a 4-week period. Two years later, her chest radiograph showed complete resolution of hilar adenopathy, and she continues to remain asymptomatic.

Discussion

The combination of erythema nodosum and hilar lymphadenopathy (Lofgren's syndrome) signals an acute presentation of sarcoidosis with a generally favorable outcome. It occurs most commonly during the spring in Caucasian women of child-

bearing age who are positive for HLA-B8:A1. Corticosteroids are rarely indicated unless pulmonary function is severely restricted, which is quite rare in Stage I disease.

Case Four—Neuroendocrine Symptoms and Advanced Stage 2 Pulmonary Disease

A 35-year-old black machine operator complained of facial numbness, headache, and chronic moderate dyspnea. A computerized tomography of his brain showed a small area of enhancement in the suprasellar region and a band of abnormal enhancement adjacent to the left frontal pole consistent with a focal infiltrative process. Chest radiograph revealed bilateral interstitial infiltrations with minimal adenopathy. Spirometric testing showed severe restrictive lung disease. The PPD was nonreactive and his SACE was 28 U/dL. Transbronchial lung and liver biopsies showed noncaseating granulomas. Further history included voluminous polydipsia and polyuria plus impotence. Neuroendocrine workup was consistent with central diabetes insipidus and panhypopituitarism.

He was treated with prednisone and replacement hormones, which lessened the dyspnea and facial numbness and improved the appearance of his chest radiograph, but the neuroendocrine deficits remained unchanged. Two months after initiation of therapy, the patient developed diabetic ketoacidosis, coma, and seizure, requiring insulin and anticonvulsant medication.

Over the subsequent 4 years, he was maintained on a gradually tapering dose of prednisone. At present, he receives 10 mg every other day, as well as testosterone and thyroid replacement therapy. His requirement for vasopressin (desmopressin acetate) has lessened considerably, and his pulmonary symptoms have essentially disappeared. No facial numbness or pain is present. Chest radiograph appears normal, SACE level is 29 U/dL, and pulmonary testing shows only minimal restrictive changes.

Discussion

Neurologic manifestations of sarcoidosis occur in 5 percent of patients with cranial neuropathy, the most common clinical presentation. A peripheral seventh nerve palsy (Bell's palsy) is the single most common cranial nerve affected. Uveoparotid fever with facial nerve palsy is rare but is virtually

diagnostic of sarcoidosis. Hypothalamic dysfunction is the most common manifestation of CNS parenchymal disease, with diabetes insipidus and other neuroendocrine deficits occurring in a smaller percentage of patients.⁹ Seizures may occur, although in this patient, the seizure may have been related to ketoacidosis. Symptomatic neurosarcoidosis is a definite indication for treatment (Table 3).

The patient also complained of proximal muscle weakness, and direct sarcoid involvement may clinically resemble corticosteroid myopathy. In addition, his fifth cranial nerve involvement is distinctly unusual with CNS sarcoidosis.

It also appears that remission of granuloma formation in the hypothalamic area occurred as reflected by the patient's gradual lack of requirement for vasopressin.

Table 3. Major Indications for Treatment.

Respiratory (symptomatic, progressive)
Ocular (uveitis)
Cardiac (arrhythmias, heart failure)
Cutaneous (lupus pernio)
Hypercalcemia
Neurosarcoidosis

Case Five—Asymptomatic with Stage 2 Pulmonary Disease

In 1971, a 35-year-old black woman who was without pulmonary complaints or symptoms had an abnormal chest radiograph with bilateral hilar and mediastinal masses, as well as interstitial infiltrates in both lung fields. Her chest radiograph 4 years earlier showed left hilar adenopathy only. Spirometric testing demonstrated mild restrictive and minimal obstructive changes. Her PPD skin test was nonreactive, and the only blood abnormality was a slight increase in beta globulins. Scapular node biopsy revealed coalescent noncaseating granulomas with giant cells. Acid-fast bacillus stains were negative, and the biopsy was consistent with sarcoidosis.

When she was 43 years of age, her SACE level was elevated (36.2 U/dL). In 1986, at age 50, her follow-up chest radiograph revealed no essential change in the presence of hilar adenopathy and parenchymal changes. She continues to be asymptomatic without receiving corticosteroids.

Discussion

The clinical course of sarcoidosis varies from a self-limited state with spontaneous resolution to a progressive, debilitating disease. The rate of spontaneous remission in Stage 2 pulmonary disease is 30 percent. Many patients will have some restrictive disease, while others will progress to Stage 3, with pulmonary fibrosis, dyspnea, and cor pulmonale. In this particular case, the radiographic appearance is essentially unchanged for more than 15 years.

The decision to treat with corticosteroids in these individuals is not clear-cut. It has been demonstrated, for example, that active sarcoid granulomas in the lungs exist in Stage 1 disease and that Gallium scan confirms their activity. Some clinicians vigorously treat Stage 1 and Stage 2 patients in an attempt to prevent alveolitis from progressing to irreversible fibrosis.¹⁰ A more conservative approach would be to treat if pulmonary infiltration or pulmonary function worsens. In addition, several factors confer an unfavorable outcome such as the presence of chronic skin lesions or bone cysts. These patients are more likely to require corticosteroid therapy.

In the case presented, the patient had no progression of her symptoms and has remained well without receiving treatment.

Case Six—Hypercalcemia and Salivary Gland Enlargement

A 61-year-old man presented with a 6-month history of an enlarging mass in the submaxillary area. Despite an otherwise asymptomatic state, routine laboratory evaluation revealed an elevated serum calcium (12.4 mg/dL; normal, 8.8 to 10.5 mg/dL) and moderately severe azotemia (creatinine, 4.2 mg/dL; normal, 0.6 to 1.2 mg/dL). His chest radiograph appeared normal.

Biopsy of the submaxillary mass revealed clusters of epithelioid cells; neck exploration demonstrated normal parathyroid glands, but a lymph node was completely replaced by nonnecrotizing granulomas and multinucleated giant cells. Corticosteroids were given, and the serum calcium was normal within 2 weeks after start of therapy. Mild azotemia remained (creatinine, 1.6 mg/dL). After 3 years, he is asymptomatic.

Discussion

Hypercalcemia occurs in approximately 10 percent of patients and may be transient and self-limiting or associated with chronic persistent sar-

coidosis. Hypercalciuria occurs in 40 percent of patients, but renal damage due to nephrocalcinosis is rare.

It has been recognized that these persons produce an increased amount of 1,25-dihydroxycholecalciferol (calcitriol), which increases calcium absorption from the gastrointestinal (GI) tract. This process is quickly reversed by low-dose corticosteroids and forms the basis for the clinically useful cortisone suppression test.¹¹

Hypercalcemia due to primary hyperparathyroidism may mimic sarcoidosis. The parathormone levels in the latter are usually normal, and the prompt response to prednisone usually clarifies the diagnosis.

A small percentage of patients (less than 10 percent) will have clinical evidence of kidney involvement. Direct granulomatous involvement is distinctly rare, but glomerulonephritis and nephrocalcinosis can produce serious impairment. In this case, it is speculative whether the patient has had kidney damage due to one of the above causes.

Case Seven—Massive Splenomegaly, Hypercalcemia, and Abnormal Chest Radiograph

A 48-year-old white postal employee underwent a routine chest radiograph in 1968 that revealed hilar adenopathy. Scalene node biopsy was consistent with sarcoidosis, and he was treated with prednisone for one and a half years at another facility.

In 1975, at the age of 55, he experienced weight loss, night sweats, and massive splenomegaly. His chest radiograph showed bilateral interstitial infiltrates and hilar adenopathy. The bone marrow biopsy showed numerous noncaseating granulomas, and he was treated with prednisone for 1 year with prompt cessation of the night sweats and reduction of the enlarged spleen to normal size within 4 to 6 weeks. He remained well until 1981 when he developed nausea, vomiting, polyuria, fatigue, and moderate splenomegaly. Routine lab tests revealed that the serum calcium was 13.5 mg/dL and creatinine was 3.4 mg/dL. The chest radiograph was essentially unchanged from 1975. His SACE level was elevated to 48.1 U/dL. He was treated with prednisone, and the serum calcium returned to normal within 1 week. There was marked improvement of the renal function over the ensuing 2 to 3 weeks. The follow-up

SACE level was 10.5 U/dL. Maintenance prednisone was continued for 6 months, and he has done well without any recurrence of sarcoid-related problems except for transient hypercalcemia in 1983, which improved spontaneously without treatment.

A follow-up chest radiograph in 1986 continued to demonstrate interstitial infiltrates, and pulmonary testing showed moderate mixed obstructive and restrictive changes despite a paucity of subjective pulmonary symptoms.

Discussion

Mild splenomegaly occurs in 20–30 percent of cases and responds promptly to corticosteroid therapy. Massive enlargement can occur with the development of hypersplenism. Asymptomatic liver involvement can be detected with cholestatic-type biochemical pattern, although jaundice is unusual.

Spontaneous improvement can occur in up to 30 percent of patients with Stage 3 pulmonary findings. A long-term beneficial effect of corticosteroids on pulmonary function has not been clearly demonstrated, although treatment for such complications as hypercalcemia, hypersplenism, or symptomatic dyspnea may be required.¹² This patient has been treated intermittently over the course of 20 years with prednisone. Long-term continuous therapy generally is not required or advisable for the vast majority of patients.

In the case presented, hypercalcemia spontaneously resolved on one occasion, although it did require prednisone for 6 months at an earlier date. In some patients, avoidance of sunlight and a low-calcium diet may be sufficient therapy to control hypercalcemia.

Summary

The introduction of Gallium-67 scintigraphy and the determination of the proportion of helper T-lymphocytes recovered by BAL have been suggested as predictive techniques to assess disease activity in sarcoidosis.¹³ In none of the cases presented were these methods used, and despite these advances, the majority of patients can be managed using spirometric testing, SACE measurement, and clinical evaluation.¹⁴

The course and prognosis of sarcoidosis frequently parallels the mode of onset. An acute onset of erythema nodosum and polyarthralgia, for

example, augurs an excellent prognosis with spontaneous resolution the general rule. Insidious onset pulmonary disease, especially in the presence of skin or bone disease, reflects the other end of the clinical spectrum, the chronic progressive course. Fortunately, cor pulmonale and respiratory failure occur in less than 5 percent of cases.

The decision when to use corticosteroids in sarcoidosis has been controversial. It has not been demonstrated, for example, that therapy influences or alters the radiographic appearance of sarcoidosis. Nevertheless, treatment is advised if progressive pulmonary symptoms develop in order to prevent the development of fibrosis and its complications. There is little controversy that certain extrathoracic disease manifestations require therapy (Table 3). Evolving concepts of immune dysfunction in sarcoidosis may eventually help to identify subsets of patients who may require and benefit from treatment early in the course of their disease. Finally, the case reports presented in this article support recent large surveys that seem to indicate the generally favorable outcome for the majority of patients identified and followed in the nonreferral setting.¹⁵

References

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GLEANINGS FROM A COMMONPLACE BOOK — *NJP*

"The more cant there is in politics, the better. Cant is nothing in itself; but attached to even the smallest quantity of sincerity, it serves like a naught after a numeral, to multiply whatever of genuine good-will may exist. Politicians who cant about humanitarian principles find themselves sooner or later compelled to put those principles into practice — and far more thoroughly than they had ever originally intended. Without political cant there would be no democracy. Pecksniff, however personally repulsive, is the guardian of private morality. And if it were not for the intellectual snobs who pay — in solid cash — the tribute which Philistinism owes to culture, the arts would perish with their starving practitioners. Let us thank heaven for hypocrisy."

A. Huxley

"To each his sufferings; all are men,
Condemn'd alike to groan;
The tender for another's pain,
Th' unfeeling for his own."
Wordsworth

"A writer is so rarely inspired as when he talks about himself."
A. France

"The capacity of academicians to be drearisome amounts to genius."
Pisacano

"Because they knew how to practice their own trade, they considered themselves clever and wise in other fields as well. But they were not so then, nor are they today. That a scientist is able to construct an apparatus and to predict correctly what it will accomplish does not mean that he is also the man to put the world in order."

Socrates