Gallium-67-Citrate Scanning in the Assessment of Disease Activity in Sarcoidosis

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From the Case Records of the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

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CLINICAL HISTORY

A 35-yr-old white female was diagnosed as having sarcoidosis 2 yr ago. At that time, she noticed that her legs were swollen and red and she was hospitalized for evaluation. She was initially treated for a presumed vascular disease in her leg, but when she did not respond to this therapy, other diagnoses were entertained. A chest x-ray suggested an enlarged right hilum and a CAT scan showed hilar and mediastinal adenopathy. A diagnostic mediastinoscopy was performed which demonstrated noncaseating granuloma. Pulmonary function studies obtained at that time demonstrated a slight reduction in lung volumes with a normal diffusing capacity. At the time of her diagnosis, she was started on prednisone (60 mg a day), which was decreased to 20 mg a day over the ensuing 18 mo. On reassessment at that time (6 mo prior to this evaluation), it was felt that her sarcoidosis was inactive and the prednisone was further tapered to 5 mg every other day. At the time of this evaluation, approximately 2 yr after her initial diagnosis, she complained of mild dyspnea on exertion but denied any cough or chest pain. She still has some discomfort and occasional swelling in her legs.

On physical examination, her blood pressure was 120/90, her oral temperature was 99.5°, her pulse was 92 per min and regular, and her respiratory rate was 18 per min. She weighed 242 pounds. Her head, ear, eye, nose, and throat examinations were unremarkable. Her chest was clear to auscultation and percussion. Her cardiac examination was normal without any murmurs, rubs or gallop. Her abdomen was normal on palpation without any detectable hepatosplenomegaly. She had mild pitting edema of both lower extremities with healed scars and mild erythema.

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Laboratory evaluation revealed a hemoglobin of 14.3 g, a hematocrit of 41%, a white blood cell count of 7000 and a platelet count of 333,000 per mm^3. Her serum chemistry was normal, including a calcium level of 9.2 g/dl. Her serum angiotensin converting enzyme (ACE) was normal at 43 units.

Review of chest x-rays obtained over the past 4 yr showed that the radiographs up to 2 yr ago were normal. Approximately 2 yr ago, she developed a prominence of the hila, particularly on the right side. This was confirmed on a chest CT scan, which also demonstrated right paratracheal and subcarinal adenopathy. A repeat chest x-ray obtained 6 mo after steroid therapy showed a decrease in size of the right hilum. There is no apparent adenopathy on current films.

Pulmonary function testing, performed at the time of initial diagnosis, demonstrated a forced vital capacity of 84%, a total lung capacity of 72% of predicted values and a normal diffusing capacity. Repeat pulmonary function testing at the time of this evaluation demonstrated her total lung capacity to be 92%, the vital capacity to be 91%, the FEV1 to be 92%, an MVV of 115% and a diffusing capacity of 82% of predicted values, and a FEV1/FVC ratio of 84%. These results are all normal.

Based on physical examination and laboratory screening, including repeat pulmonary functions testing, it was felt that there was no evidence of active sarcoidosis. However, to further confirm this clinical impression, a gallium scan was ordered (Figs. 1 and 2).

DISCUSSION

Sarcoidosis is a chronic granulomatous disease of uncertain etiology and pathogenesis which can involve almost any organ in the body, although pulmonary manifestations often predominate (*1,2*). The diagnosis is often one of exclusion, although the confirmation of noncaseating granulomas in the absence of evidence of vasculitis, or fungal or mycobacterial disease is considered diagnostic. The clinical findings of sarcoidosis vary considerably. With respect to pulmonary manifestations, asymptomatic presentations with incidental recognition of radiographic abnormalities are, in fact, most common. When patients

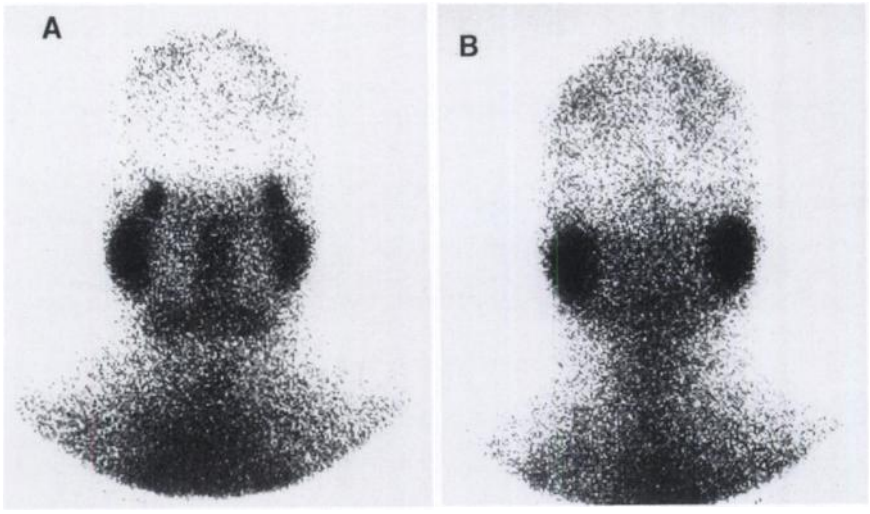

FIGURE 1. Anterior (A) and posterior (B) images of the head and neck area demonstrate intense uptake of ^{67}Ga-citrate in the parotid glands bilaterally. This finding is suggestive of sarcoidosis.

present with respiratory complaints, nonspecific symptoms such as cough, dyspnea or chest discomfort predominate. Spontaneous remission occurs in over 50% of cases, but in a significant number of patients the disease continues to progress causing permanent lung injury and respiratory insufficiency. Therefore, detecting and assessing disease activity in the lung is of paramount clinical importance in the management of these patients.

Sarcoidosis is observed world-wide, however, its incidence is poorly defined. In the U.S., it is felt to occur in somewhere between one in ten thousand and one in twenty-five thousand individuals; blacks appear to have an incidence approximately 10 times greater than that of whites (*3*). Of all patients with sarcoidosis, there is a three to two female-to-male predominence. The peak incidence occurs between the ages of 20 and 40. Although sarcoidosis occurs at all ages, it is rare in children and in adults over the age of 70.

The vast majority of patients with sarcoidosis are asymptomatic and may not even be diagnosed (*4,5*). Of those diagnosed, approximately 25%–30% are asymptomatic despite the finding of an abnormality, most often an abnormal chest x-ray. Twenty to 40% present with nonspecific pumonary symptoms such as shortness of breath, dyspnea on exertion, cough, or chest discomfort. Up to 40% of patients present with systemic symptoms such as fever, anorexia, weight loss, fatigue, or myalgias. Between 10% and 30% of patients manifest skin lesions; erythema nodosum is the most common cutaneous manifestation.

Intrathoracic involvement with sarcoidosis is by far the most frequent localization of disease activity, occurring in about 90% of patients. The intrathoracic manifestations of the disease may consist of hiliar or mediastinal adenopathy, interstitial or alveolar pulmonary infiltrates, endobronchial granuloma formation, or pulmonary fibrosis. Pleural involvement is quite unusual. Pulmonary function derangements progress as intrathoracic involvement worsens. The most common finding is a restrictive pattern with a gas transfer abnormality (abnormal diffusing capacity). However, obstructive lung disease and bronchial hyperreactivity can also be seen.

Extrathoracic manifestation of sarcoidosis can involve almost any organ in the body (*2*). The spleen is involved in about 75% of patients, but is enlarged in only 20%. Hepatic involvement is slightly less common than splenic involvement. Hepatomegaly may be seen in 20% of pa-

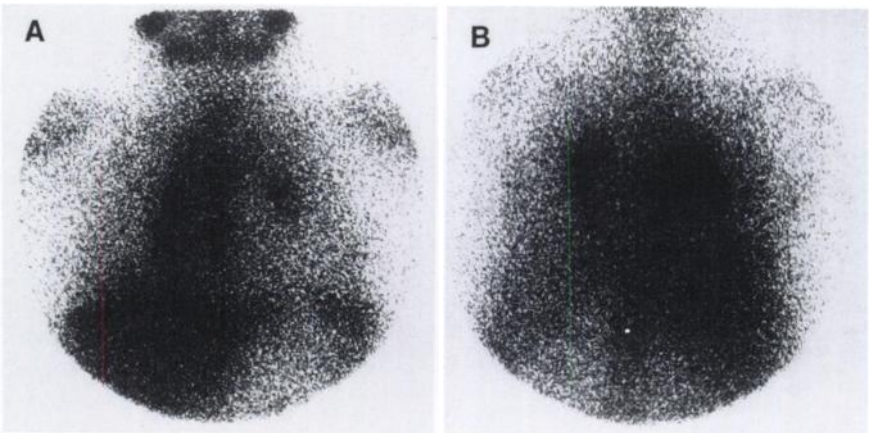

FIGURE 2. Anterior (A) and posterior (B) scans of the chest and the upper abdomen reveal visualization of the hilar nodes bilaterally. This finding, along with that noted in Figure 1, strengthens the diagnosis of an active disease process.

tients with sarcoidosis, however, granulomatous infiltration of the liver identified histologically occurs more often. Approximately 70% of patients have granulomas demonstrated on liver biopsy and as many as 50% will have abnormal liver function tests. Muscle involvement is also quite common. Infiltration and granulomas can be demonstrated in 50% to 80% of patients on biopsy, however, the majority of patients are asymptomatic. In rare cases, a granulomatous myositis may be present.

Skin involvement may be present in up to 40% of patients. Erythema nodosum occurs in up to 20% of patients. It is important to remember that this is a nonspecific finding and biopsies of these lesions will not demonstrate granulomas. Less frequently, patients may manifest specific cutaneous findings of sarcoidosis. This is most often lupus pernio; violaceous plaque-like lesions on the nose or cheek. Patients may also manifest nodules, plaques, maculopapular eruptions or enlargements of preexisting scars.

Ophthalmic involvement is also frequent, most often manifesting as anterior segment disease. All patients with sarcoidosis require a careful ophthalmologic examination to detect granulomatous conjunctivitis or chronic granulomatous uveitis. Posterior segment disease, orbital and other ophthalmic manifestation can also occur.

Other organs that may be involved include the large joints in 10%–15% of patients, and the bones in under 5% of patients. The central nervous system is involved in 5%–10% of patients, most often presenting as cranial neuropathy (particularly cranial nerves VII, II, IX and VIII) or aseptic meningitis (lymphocytic pleocytosis with increased protein).

Hypercalciuria is quite frequent and occurs in up to 60% of patients. Hypercalcemia is less common and occurs in under 20% of patients. These abnormalities of calcium metabolism are secondary to hyperabsorption of calcium due to overproduction of 1,25-dihydroxy-D_3 by alveolar macrophages and by the cells within the granulomas. Patients may present with nephrolithiasis or nephrocalcinosis as their initial finding. Only after review of routine chest x-rays may sarcoidosis be suspected.

The course of sarcoidosis is quite variable. Approximately one-half to two-thirds of patients resolve spontaneously with no or minor residua. However, approximately one-third of patients exhibit a smoldering or progressively worsening course and 15%–20% of patients suffer permanent loss of lung function. Somewhere between 1%–5% of patients die due to respiratory failure, most often in the setting of cor pulmonale and right heart failure. Cardiac and neurologic involvement may also be a cause of death in sarcoidosis. Because of the significant morbidity and potentially fatal outcome associated with sarcoidosis, it is important that both the diagnosis and the extent and severity of organ involvement be established in all patients with this disorder.

The diagnosis of sarcoidosis requires suggestive clinical manifestation, histologic demonstration of noncaseating granulomas, and the lack of evidence for other causes of granulomatous inflammation. This can usually be accomplished with history and physical examination, examination of biopsy specimens for vasculitis, fungus, mycobacteria, and foreign bodies, as well as by culturing the biopsy and respiratory secretions for various organisms. To establish diagnoses, other tests, such as determination of the serum ACE level, bronchoalveolar lavage to assess inflammatory response and the presence of lymphocyte subsets within the lung and ^{67}Ga scanning, may be helpful, but are not diagnostic. Gallium-67 scanning may help to localize sites of extrapulmonary involvement, particularly the salivary glands, for directed biopsy. Overall, the diagnostic yield on blind biopsies of the lacrimal or minor salivary glands is under 25%. However, if these glands are enlarged or active on a ^{67}Ga scan, then the diagnostic yield may be up to 60%. Despite this aspect, the major apparent utility of ^{67}Ga scanning in patients with sarcoidosis is its assessment of disease activity.

Assessing Disease Activity Within the Lungs

It is commonly believed that the earliest pulmonary lesions of sarcoidosis consist of a mononuclear cell interstitial inflammation of "alveolitis" (*6,7*). This lesion is followed by granulomas that are characteristic of the disease. While in the majority of patients these granulomas subsequently resolve leaving relatively normal tissue, in some patients fibrosis ensues.

The clinical symptoms and x-ray abnormalities observed in patients with sarcoidosis can be the result of either the inflammatory response or the subsequent fibrosis. However, the implications, in terms of treatment, are quite different depending on the underlying pathologic process. Abnormalities resulting from inflammatory processes are potentially reversible, while those that are due to fibrosis will not respond to treatment. The usual treatment for sarcoidosis consists of the administration of corticosteroids as anti-inflammatory agents. Since these drugs can themselves have significant side effects, it is important to differentiate those patients with inflammatory lesions who can be offered treatment from those with irreversible lesions who should not receive corticosteroids and their concomitant side effects. For the assessment of the activity of inflammation, neither age, symptoms, laboratory examinations, pulmonary function testing nor x-ray findings have been useful in adequately differentiating inflammatory lesions from those due to fibrosis. Also, none of the diagnostic modalities or clinical signs and symptoms adequately detects early inflammatory lesions.

Over the past two decades, several methods have been proposed for assessing pulmonary disease activity in patients with sarcoidosis. These have included measuring serum ACE levels, bronchoalveolar lavage, and ^{67}Ga-citrate scanning.

ACE cleaves two terminal amino acids from angiotensin-1 converting it to angiotensin-2. In normal subjects,

this enzyme is produced by the endothelial cells; in sarcoidosis, it is produced by both endothelial cells and by the epithelioid cells of granulomas. The ACE level is increased in 50%–80% of patients with sarcoidosis. However, its level is also elevated in 2%–3% of normals and in patients with any one of a number of other disorders, including Gaucher's disease, leprosy, amyloid, myeloma, lymphoma, histoplasmosis and some cases of alcoholic hepatitis. It is felt that in sarcoidosis the ACE level reflects the total-body granuloma load and not just the pulmonary granuloma load. However, many investigators feel that the ACE level reflects disease activity because these levels are often seen to rise in patients in whom disease is flaring and these levels fall in patients who have spontaneous or steroid-induced remissions of disease activity (*8,9*).

Bronchoalveolar lavage is a technique in which a bronchoscope is wedged in a subsegmental bronchus, aliquots of saline are introduced and then suctioned out, and the total cell return and differential of the return cells is then determined. In normal states greater than 90% of the cells recovered by bronchoalveolar lavage are alveolar macrophages, less than 10% are lymphocytes (with 65%–85% of these being T-lymphocytes), and less than one percent are polymorphonuclear leukocytes or eosinophils. In sarcoidosis, there is a significantly increased total cell recovery with an increase in the absolute number of alveolar macrophages. Generally, there is an increase in both the number of recovered lymphocytes (mostly T-cells) and in their proportion compared to the other types of cells. The mononuclear cells that are recovered are activated; this is evidenced by their spontaneous production of chemotactic factors and other mediators. In the fibrotic stages of sarcoidosis, there may be an increased percentage of polymorphonuclear cells and eosinophils recovered in the brochoalveolar lavage fluid. There remains considerable controversy as to whether or not the bronchoalveolar lavage findings can be used to predict either clinical course or response to steroids, although many investigators advocate using an elevated percentage of T-lymphocytes in the total lavage differential as an indication for treatment (*2,10–13*).

Gallium-67-Citrate Imaging

Radionuclide scintigraphy with ^{67}Ga-citrate has been advocated for the assessment of disease activity in sarcoidosis (*11,14–16*). The radiopharmaceutical is injected intravenously and is taken up by mononuclear phagocytes within the lungs and in other involved organs in patients with active sarcoidosis. Within the lungs, the alveolar macrophages are the primary inflammatory cells that incorporate ^{67}Ga. Uptake of ^{67}Ga within the lung has been advocated as a useful technique for separating fibrotic changes from active inflammatory disease. Gallium-67 imaging may also be helpful in localizing nonpulmonary cites of disease activity as well as identifying actively involved hilar and mediastinal nodes (*17–19*). The major advantage of this imaging technique is that it is noninvasive and can be performed serially. To be of maximum benefit, ^{67}Ga scans, if possible, should be interpreted in a quantitative manner (*20*). The major drawback is that ^{67}Ga uptake is nonspecific making it difficult to quantitate the precise amount of tracer uptake.

Although increased pulmonary uptake of ^{67}Ga is not specific for sarcoidosis, increased pulmonary uptake of the radiotracer has been found in approximately two-thirds of patients with sarcoidosis and has been reported to occur in over 90% of active cases (*21*). The argument that ^{67}Ga imaging may be useful in distinguishing active granuloma formation and/or alveolitis from fibrotic changes has been supported by studies demonstrating negative ^{67}Ga scans in 68%–87% of dormant cases (*21,22*). There remains controversy as to whether or not increased pulmonary uptake of ^{67}Ga correlates with either the degree of inflammation, serum ACE levels or the percent of lymphocytes obtained on bronchoalveolar lavage. Proponents feel that ^{67}Ga uptake correlates well with disease activity and is more sensitive than serum ACE for following disease activity. Several studies have shown a correlation between the degree of uptake on serial ^{67}Ga scans with the level of response to therapy with corticosteroids, both early in treatment and after 1 yr of therapy (*11,12*).

In this patient, the gallium scan demonstrated significant uptake both within the lungs and at extrathoracic sites (Figs. 1 and 2). This was an important observation which was noted despite the relative paucity of symptoms, physical findings, or laboratory abnormalities, and despite the fact the patient had been maintained on corticosteroids for 2 yr, although she had been on a tapering course over the previous 6 mo. Because of this patient's relative clinical stability and normal pulmonary function tests, therapy was not increased solely on the basis of the ^{67}Ga scan findings. However, since the scan findings do suggest disease activity, the patient will be followed more closely over the next few months than had not a gallium scan been obtained. There are no other well accepted, noninvasive techniques that are of use in assessing sarcoidosis activity or that can be used to confirm ^{67}Ga scan findings. However, the role of high-resolution CT scanning is being studied (*23,24*). Bronchoalveolar lavage may also help to assess sarcoidosis activity, but it is an invasive procedure. In this patient, ^{67}Ga scan was the only study that pinpointed disease activity. The scan findings heightened our concern and have altered the manner and closeness with which we will follow this patient. The development of any new symptoms or laboratory findings, especially any deterioration in pulmonary function tests, will warrant reinstitution of higher doses of corticosteroids.

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