Clinical Correlations of Serum Angiotensin-Converting Enzyme (ACE) in Sarcoidosis*

A Longitudinal Study of Serum ACE, "Gallium Scans, Chest Roentgenograms, and Pulmonary Function

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Thirty-one patients with biopsy-confirmed sarcoidosis were studied for two to four years to compare serum angiotensin-converting enzyme (ACE) levels to clinical status, "gallium scans, chest x-ray films, and pulmonary function tests (PFTs). Serum ACE levels and changes in ACE level correlated best with the clinical status of patients and their gallium scans (p<0.0005), and less with their chest x-ray films (p = 0.012) or PFTs (p = 0.007). The gallium scan was especially useful for localizing areas of disease involvement. Serial measurements of serum ACE were found to be a sensitive means for following the clinical course of patients with sarcoidosis and at times for predicting clinical relapse or improvement.

A diagnosis of sarcoidosis usually requires the demonstration of noncaseating, epithelioid cell granulomas in at least one tissue, plus clinical evidence of multiple organ involvement. However, various clinical and laboratory tests have been found helpful for supporting this diagnosis, including a Kveim test, "gallium scan, chest roentgenogram, skin tests for anergy, pulmonary function tests, studies of bronchoalveolar cells, and a measurement of serum angiotensin-converting enzyme (ACE). Of these tests, the serum ACE assay may be the simplest, most readily available, and most helpful, even though its specificity is not absolute. The presence of an elevated serum ACE level in a patient suspected of having sarcoidosis is in general supportive of this diagnosis.

In addition to diagnosis, serial assays of serum ACE appear to be useful in evaluating the clinical course of the disease and the response to steroid therapy, and especially for detecting impending clinical relapse. The purpose of this study was to test the possible correlation of serum ACE measurements with clinical findings, "gallium scans, chest x-ray films, and pulmonary function tests (PFTs) in patients with active sarcoidosis who were being followed longitudinally and where each modality was being evaluated independently.

No current test for sarcoidosis activity can be considered as the "gold standard" for this disease.

Material and Methods

Study Population

Thirty-one patients were studied in whom a diagnosis of sarcoidosis was supported by a biopsy showing noncaseating granulomas in at least one organ (usually the lung by transbronchial biopsy). Twenty-nine of these had pulmonary involvement as well as involvement of parotid glands, lacrimal glands, liver, skin, joints, spleen, or uveitis. Nine had stage 1 lung disease by chest x-ray film, ten, stage 2; ten, stage 3; and 2, stage 0. These patients were evaluated at regular intervals over a two- to four-year period. Nineteen patients were treated with prednisone either continuously or at some time during their course, whereas corticosteroids were not indicated in 12 other patients. Prednisone was administered initially in dosages of 20 to 60 mg on alternate days. Very sick patients with severely impaired ventilation were given daily steroid doses until ventilation improved. When the disease stabilized, the dosage was tapered to a maintenance level.

Ages ranged from 18 to 71 years, with a mean age of 37 years for the steroid group and 40 years for the nonsteroid group. Twenty-nine patients were black, one was Oriental, and one was white. Twenty-six patients were women, and five were men.

The patients were seen on an average of every four weeks for the clinical evaluation and assessment of disease activity. Patients were judged as being stable, worse, or improved by two independent clinicians. These judgments were based upon an overall clinical impression without any attempt to numerically quantitate the clinical status. Patients were questioned about subtle, nonspecific symptoms such as nasal obstruction, headache, malaise, loss of

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appetite, weight loss, and night sweats, as well as more severe manifestations of sarcoidosis such as shortness of breath, cough, wheezing, chest pain, glandular enlargement, ocular inflammation, skin changes, arthritis, fatigue, palpitations, and hemoptysis. On physical examination, special attention was given to auscultation of the chest and palpation of the liver and spleen. The result of the current serum ACE level was not immediately available to the clinician. Serum ACE levels were determined at each visit, whereas PFTs and chest x-ray films were obtained every four months and gallium scans every six months; if disease reactivation was suspected clinically, a scan and chest roentgenogram were obtained immediately.

Laboratory Studies

Clotted blood (7 ml) was obtained from each patient for serum ACE assay performed by Lieberman’s modification13,14 of the method of Cushman and Cheung.15 Normal values for serum ACE are 22.8±6.0 U/ml. In this study, values of 35 U/ml or higher were considered abnormal. Only changes in ACE values of ±10 percent (the limits of laboratory variation for the assay procedure) were considered significant, but serial trends were considered more meaningful than any individual serum ACE value.

The Ga imaging was obtained at Martin Luther King Medical Center (F.S.M.) 72 hours after the intravenous administration of 4 mCi of 67Ga citrate. Images were obtained from head to thigh with a dual rectilinear scanner with a 20 cm diameter crystal using medium-energy, medium-resolution collimators, with the spectrometer set to accept gamma energies from 150 to 450 KeV. In addition, some patients were imaged using a large field of view Anger camera equipped with a high energy collimator. The spectrometer was set to accept 184 KeV photons. Activity accumulation was judged abnormal when it exceeded activity in the soft tissues of the shoulder; activity less than that in the liver was graded as 1 plus; activity equal to that in the liver was 2 plus; activity exceeding hepatic activity was 3 plus. These semi-quantitative scans were considered to be associated with an acceptable level of diagnostic radiation exposure. The overall evaluation of the gallium scan related to the intensity and distribution of gallium uptake by the lung, plus the number of other sites showing uptake (spleen, parotid, orbits, etc).

The PFTs included measurement of lung volumes, flow rates, distribution of ventilation, and gas transfer index (Dco, single breath method). Of these tests, the vital capacity, total lung capacity, forced expiratory volume in 1 second, and the diffusing capacity were closely evaluated for worsening, improvement, or lack of change. A 10 percent absolute change (percent of normal) was considered to be significant. Where changes occurred, it was obvious that the Dco measurement was the most revealing and sensitive in this group of subjects, so that much of the evaluation was actually based upon this measurement.

Chest x-ray films (PA and lateral) were reviewed by the radiologist and compared to previous films so that they could be judged as unchanged, worse, or improved.

Correlation of Clinical Modalities with Changing Patterns of Serum ACE

Patterns of changing levels of serum ACE were identified for each patient comprising three to ten successive ACE values over periods of four to 32 months (12±6.7 months; n = 43). Drops in ACE level ranged from 14 to 103 U/ml (mean = 43.15±22.7 U/ml; n = 26) and the increases ranged from 18 to 152 U/ml (mean = 41.9±30.2 U/ml; n = 21). The majority of these changes in ACE level (35 of 47) went either to or from a normal value. Eleven changes occurred entirely within the abnormal range of values and one within the normal range.

The statistical analysis of these data utilized chi square with six cells. The calculation of chi square may be inaccurate since the "expected number" for some of the cells was less than five.

RESULTS

Initial Serum ACE Values

The initial mean serum ACE value for the 31 patients with active sarcoidosis was 47.5±23 U/ml (±SD). Those patients requiring corticosteroid therapy had a mean value of 51.4±27 U/ml compared to 41.1±12 U/ml (not statistically significant) for those patients not requiring such therapy. This contrasts to the mean of 22.6±6 U/ml for 172 control subjects reported previously from this laboratory.16 The difference in serum ACE between patients with sarcoidosis and control subjects is highly significant (p<0.001).

Comparison of Serum ACE to Other Clinical Modalities

Patterns of rising or falling serum ACE levels were compared to concurrent or immediately-ensuing evaluations of patients with sarcoidosis by the four clinical modalities (Table 1). A rising serum ACE pattern correlated best with (1) worsening clinical status (85.0 percent) and (2) a worsening gallium scan (94.0 percent). Only one of 16 gallium scans was interpreted to be improving in the presence of a rising serum ACE level. Falling serum ACE patterns were associated with improved clinical status in every instance and with improved gallium scans in 92 percent of cases. Statistically, these correlations were highly significant (p<0.0005).

Worsening or improvement of the chest x-ray film and PFTs was not as highly correlated with changing patterns of serum ACE levels as was the clinical evaluation or gallium scan; most of the PFTs and chest x-ray films were read as "unchanged" in spite of clinical worsening or change of serum ACE level. The chest

Table 1—Rising and Falling Patterns of Serum ACE Levels

<table>
<thead>
<tr>
<th>Serum ACE Pattern</th>
<th>Status of Clinical Modality</th>
<th>Improved</th>
<th>No Change</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rising</td>
<td>Clinical status</td>
<td>0</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Gallium scan</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Chest x-ray film</td>
<td>0</td>
<td>15</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PFT</td>
<td>0</td>
<td>15</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Falling</td>
<td>Clinical status</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gallium scan</td>
<td>24</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray film</td>
<td>8</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PFT</td>
<td>9</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chi Square</td>
<td>p</td>
<td>&lt;0.0005</td>
<td>0.012</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Both treated and untreated patients are included.

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roentgenograms and PFTs were usually abnormal whenever lung disease was present, but changes in the chest x-ray film findings or PFTs were not always observed in parallel with subsequent clinical change or with the pattern of changing serum ACE level. The significance of the chest x-ray films or PFT observations was less than for clinical status or gallium scan (chest x-ray film: p = 0.012; PFTs: p = 0.007).

Examples of Serum ACE Correlations in Three Patients

Case 1

This 35-year-old black woman with sarcoidosis illustrates discordance between the serum ACE levels and either the chest roentgenograms or PFTs, in contrast to concordance between the serum ACE levels and gallium scans. During the initial acute stage of this patient's disease, a gallium scan showed intense generalized uptake in the lung parenchyma and mediastinum (Fig 1). The chest x-ray film, on the other hand, showed only bilateral hilar adenopathy without infiltrates (Fig 2). The PFTs were always normal, although improved when the disease was under control in 1980 (Table 2). A very high serum ACE level of 106 U/ml was obtained when the gallium scan was highly positive (Fig 3).

Table 2—Pulmonary Function Data for Case 1

<table>
<thead>
<tr>
<th></th>
<th>9/78 (%)</th>
<th>1/80 (%)</th>
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</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>3.38 (97.1)</td>
<td>3.66 (100.8)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.60 (90.3)</td>
<td>3.19 (120)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.23 (109.6)</td>
<td>5.89 (112.9)</td>
</tr>
<tr>
<td>MBC (L/min)</td>
<td>104 (81.2)</td>
<td>127 (121)</td>
</tr>
<tr>
<td>Dco (ml CO₂ STPD/min/mm Hg)</td>
<td>23 (82.1)</td>
<td>21.4 (88.1)</td>
</tr>
</tbody>
</table>

Clinical Correlations of Serum ACE in Sarcoidosis (Lieberman et al)
Table 3—Pulmonary Function Data for Case 2

<table>
<thead>
<tr>
<th></th>
<th>8/77 (%)</th>
<th>5/79 (%)</th>
<th>11/79 (%)</th>
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</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>2.71 (93.5)*</td>
<td>2.85 (95)</td>
<td>2.91 (93.9)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.06 (89.2)</td>
<td>2.33 (100)</td>
<td>2.25 (94.9)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>3.65 (78.8)</td>
<td>4.16 (83.8)</td>
<td>3.69 (79.7)</td>
</tr>
<tr>
<td>MBC (L/min)</td>
<td>129 (130)</td>
<td>136 (154)</td>
<td>134 (150.6)</td>
</tr>
<tr>
<td>Dco (ml CO₂, STPD/ min/mm Hg)</td>
<td>16.7 (68.2)</td>
<td>21.4 (107)</td>
<td>20.3 (97.5)</td>
</tr>
</tbody>
</table>

*Percent of normal.

Case 2

This 51-year-old black woman illustrates the course of a patient with sarcoidosis who was treated with corticosteroids and achieved a clinical remission associated with normalization of the serum ACE and gallium scan, stabilization of the chest roentgenogram, and improvement of the Dco (Table 3). Approximately one year later, a rising serum ACE level preceded a clinical relapse which was associated with an abnormal gallium scan and increasing infiltration on chest x-ray film, whereas the PFTs remained unchanged. An increase in dosage of prednisone again brought the disease into remission, and the serum ACE level receded back to normal (Fig 4).

Case 3

This 42-year-old black man with proven sarcoidosis had initial ACE values of 65 to 95 U/ml when he entered the study, although he was entirely asymptomatic (Fig 5). The PFTs showed moderate restriction with an abnormal Dco (58 percent of normal) (Table 4), and the chest x-ray film showed only minimal interstitial infiltrates. The gallium scan showed abnormal uptake of gallium only by an enlarged spleen (Fig 6, left). The patient was treated with prednisone because of the splenic enlargement and fear of rupture; prednisone dosage was tapered and discontinued approximately six months later when the gallium scan of the spleen (Fig 6, center), Dco, and serum ACE were normal. Within six weeks, the serum ACE rose to 130 to 170 U/ml, and the patient developed cough and dyspnea. The PFTs and chest x-ray films were now compatible with reactivation of the disease and more severe pulmonary involvement; the gallium scan now showed uptake by the lung, the hilar areas, and the spleen (Fig 6, right). Therapy with prednisone was resumed, with reduction of serum ACE level followed by clinical improvement.

This case study shows the value of a gallium scan for demonstrating localized areas of sarcoidosis, as in the spleen, and for revealing more widespread involvement subsequently. The rise and fall of serum ACE levels correlated strongly with the clinical course; a rise in serum ACE was the earliest indicator of reactivation of the disease.

Sarcoidosis with Normal Serum ACE Levels in Two Patients

Among the 19 treated cases of sarcoidosis, one patient exhibited persistently normal serum ACE values associated with pulmonary infiltrates, hilar adenopathy (stage 2), and a positive gallium scan with uptake by both lungs. With treatment, the ACE level dropped from 25 U/ml to 16 U/ml (a 35 percent drop), the lung infiltrates cleared (now stage 1), and the gallium scan became negative. The PFTs were always normal and unchanging. In this case, a persistent drop in serum ACE level of 9 U/ml within the normal range...
Figure 6. 67Gallium scans of the patient in Figure 5. A, left: Initial scan showing abnormal uptake only by an enlarged spleen. B, center: Normal gallium scan resulting from therapy with prednisone. C, right: Reactivation of sarcoidosis following cessation of corticosteroid therapy. Scan shows uptake of \( ^{67} \text{Ga} \) by the lung, mediastinum, and spleen. This gallium scan was performed with an Anger camera, resulting in the relative difference in size of the organs as compared to the total body scan shown in left and center which were obtained with a dual rectilinear scanner.

coincided with clinical improvement.

Another untreated patient had been followed for four years with serum ACE values ranging between 28 and 34 U/ml. At one time, a single serum ACE value of 56 U/ml was obtained, associated with dyspnea, weight loss, wheezing on chest examination, and bilateral interstitial lung infiltrates. These signs and symptoms abated, and the ACE level was noted to have fallen to 30 U/ml four weeks later without treatment. The PFTs showed mild restrictive disease, stable throughout. This was the only patient to show an isolated elevation of serum ACE. More frequent testing may have disclosed a more gradual rise and fall of the serum ACE during the eight-week interval.

**DISCUSSION**

This longitudinal study of serum ACE levels in patients with sarcoidosis confirms the usefulness of this assay for reflecting relapse of the disease or clinical improvement. Serum ACE levels correlated best with either clinical assessment of the patients or the gallium scans, but in many instances, the change in serum ACE level appeared to herald subsequent changes in the other clinical modalities.

In our experience, the clinical evaluation of patients with sarcoidosis is as good as any laboratory evaluation, including serum ACE or gallium scan, for evaluating the status and course of the disease. However, the availability of a low cost confirmatory test should be extremely helpful in patient care, especially for physicians not as experienced in evaluating or treating patients with sarcoidosis as those in our group. It is not recommended that treatment be geared to the level of serum ACE, but any progressive rise of the level indicates need for close clinical observation and consideration of initiating or increasing the dosage of corticosteroid. A dropping level is a good prognostic sign.

Chest roentgenograms and PFTs were not as sensitive for reflecting short-term changes in the clinical status of these patients. Insensitivity of PFTs in this regard has been suggested previously, but adequate longitudinal studies have not been done. All patients with lung involvement in our series had abnormal chest x-ray films or PFTs, but fluctuation in these two

<table>
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<th>Table 4—Pulmonary Function Data for Case 3</th>
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<tbody>
<tr>
<td>VC (L)</td>
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<tr>
<td>FEV₁ (L)</td>
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<tr>
<td>TLC (L)</td>
</tr>
<tr>
<td>MBC (L/min)</td>
</tr>
<tr>
<td>Dco (ml CO, STPD/mm Hg)</td>
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Clinical Correlations of Serum ACE in Sarcoidosis (Lieberman et al)
procedures in parallel with either the clinical evaluation or serum ACE level was infrequent.

The gallium scan was found to be as reliable as the serum ACE level for reflecting changes in the clinical status of patients with sarcoidosis, whether the lungs were primarily involved or not. In contrast to the serum ACE level, the gallium scan was particularly useful for localizing areas of disease involvement, such as the spleen (see case example), lymph nodes, salivary glands, lacrimal glands, or eyes. The 

\[ ^{67}\text{Ga} \]

uptake is not specific for sarcoidosis, but it localizes in a variety of inflammatory and neoplastic processes. The more intense the inflammatory process, the more intense the gallium uptake. A close correlation between the serum ACE level and gallium scan has been reported previously, but gallium imaging is relatively expensive and carries with it the putative risks of radiation. A gallium scan imposes a radiation burden similar to that received from a roentgenographic examination of the gastrointestinal tract, so that it should not be employed as a routine screening study. The serum ACE test does not have any similar limitations.

Recently, bronchoalveolar lavage has been presented as another modality for evaluating activity and severity of sarcoidosis. However, the increased number of T-lymphocytes found in the bronchial washings of patients with sarcoidosis has also been seen in others with hypersensitivity pneumonitis, tuberculosis, and lymphoma. This procedure evaluates only pulmonary involvement by the disease and is of no use for those cases where the lungs are not involved. Serum ACE, on the other hand, reflects total body granulomatosis and is not dependent upon involvement of any one organ. The ACE assay also lends itself more easily to serial measurement than does bronchial lavage. Measurement of ACE level in the lavage fluid has been reported to be as useful, or possibly more sensitive than serum ACE for following the clinical course of pulmonary sarcoidosis. However, the levels of ACE found in lavage fluid are so low that differences between sarcoidosis patients and control subjects range from only 0.1 to 2.0 units. The difficulty in distinguishing between such low ACE values by currently available methods, and the need to perform lavage and to concentrate the lavage fluid prior to assay, make it doubtful that this procedure will be of practical value.

Other investigators have suggested previously that repeated assays of serum ACE are useful for following patients with sarcoidosis. Serum ACE levels have been found useful as an index for evaluating the clinical course of sarcoidosis and for predicting a relapse, as well as a means for assessing current activity and the course of sarcoidosis. Larzul et al found that serum ACE measurements help to distinguish between complete and incomplete remissions of sarcoidosis. Our suggestion that the serum ACE level was useful for monitoring the effects of corticosteroid therapy and for determining the dose and duration of such therapy has also been confirmed by others.

Most investigators believe, as we do, that the serum ACE level is helpful in supporting a diagnosis of sarcoidosis, even though the specificity is not absolute. Elevations of serum ACE are also found in patients with Gaucher's disease, leprosy, lymphangioleiomyomatosis, diabetes mellitus with severe retinopathy, alcoholic hepatic cirrhosis, and hyperthyroidism. Of these conditions, only diabetes mellitus and cirrhosis of the liver may occur frequently enough in patients suspected of having sarcoidosis as to affect the diagnostic use of the serum ACE test. However, a serum ACE determination should be used only in specific instances where a diagnosis of sarcoidosis is being considered, and not as a screening test for this disease. Serum ACE should be interpreted with knowledge of these other complicating disease states, much like the serum glutamic oxaloacetic transaminase (SGOT) is used for confirming cardiac damage when it is known that SGOT is also elevated by liver, muscle, or brain damage.

Serum ACE levels reflect total body granulomatosis in sarcoidosis and not only pulmonary involvement. Total body 

\[ ^{67}\text{Ga} \]

scans are sensitive for reflecting active sarcoidosis and are capable of localizing areas of involvement by the disease, but this procedure cannot be used for routine follow-up of patients. These studies indicate that serial measurements of serum ACE are a sensitive means for following the clinical course of patients with sarcoidosis, and at times, for predicting either clinical relapse or improvement.

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