Assessment of Activity in Sarcoidosis

Sensitivity and Specificity of $^{67}$Gallium Scintigraphy, Serum ACE Levels, Chest Roentgenography, and Blood Lymphocyte Subpopulations

Heinrich Kiech, M.D.; Horst Kohn, M.D.; Friedrich Kummer, M.D., F.C.C.P.; and Alois Mostbeck, M.D.

The value of different factors are examined to assess activity in 60 patients with biopsy-proven sarcoidosis. In patients with active sarcoidosis ($n=35$), $^{67}$Gallium scans proved to be the most sensitive method (94 percent sensitivity), followed by serum angiotensin I converting enzyme (S-ACE) levels, chest x-ray films, and lymphocyte assays. In patients with peripheral pulmonary lesions, chest x-ray films failed in 32 percent of cases to document activity (68 percent sensitivity) whereas $^{67}$Ga lavage together with a decrease of circulating blood T-lymphocytes, have been described as an indicator of disease activity.$^{11-18}$

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by an enhanced cellular immune response at sites of involvement. Spontaneous remission of the disease, mainly in newly developed cases, can be observed. However, in some cases, treatment with corticosteroids is necessary either for the relief of symptoms or for the prevention of irreversible dysfunction of involved organs.

Necessarily, for the clinical management of patients with sarcoidosis, the evaluation of activity of the disease is of great importance which often raises problems both in definition and grading of activity, as well as in therapeutic decisions. Sometimes conventional criteria such as clinical symptoms or chest x-ray film changes in patients with proven sarcoidosis fail to document activity.

During recent years, various efforts have been made to establish reliable and noninvasive means for assessment of disease activity in pulmonary sarcoidosis. Previous reports have focused attention on serum angiotensin I converting enzyme (S-ACE) assays and gallium scanning as potential aids in diagnosis and evaluation of activity.$^{1-10}$ Changes in T-lymphocyte immune system in patients with sarcoidosis, such as significant enhancement of activated lung T-lymphocytes on sites of granuloma formation assessed by bronchoalveolar scans and S-ACE levels remained to give reliable results. Despite poor specificity, negative $^{67}$Ga scans together with normal ACE levels have a high predictive value for exclusion of active sarcoidosis. In patients with peripheral pulmonary lesions, chest roentgenography is of doubtful value for staging lung involvement and assessment of activity including monitoring and control of therapy.

Patients and Methods

Sixty patients with histologically-proven sarcoidosis were selected for this study; 39 were women, 21 patients were men. Their ages varied between 17 and 71 years. All patients were white.

Definition of activity

Activity of sarcoidosis was defined by clinical symptoms such as fever, cough, dyspnea, arthralgia, chest pain, etc., together with or without pathologic chest roentgenographic findings. Activity was also suggested in clinically asymptomatic patients, but with undoubted and marked roentgenographic deterioration. Additionally, patients with major manifestations such as recently developed skin lesions, parotid or ocular involvement, lymphadenopathy, or deterioration of lung function, were regarded to have active disease.

Inactive sarcoidosis was suggested in cases with absent clinical symptoms together with a negative or nonprogressive chest x-ray film. According to these criteria, 35 patients were regarded to have active sarcoidosis, whereas 25 patients had inactive sarcoidosis.

To evaluate differences between various types of active sarcoidosis, these patients ($n=35$) were divided into two groups as follows:

1. One group ($n=13$) with only hilar lymph node enlargement (radiologically type I). Most of these patients had recently developed and diagnosed sarcoidosis.

2. The other group ($n=22$) consisted of patients with various and heterogenous manifestations of active sarcoidosis showing lesions in the periphery of the lung (radiologically type II or III) or extrapulmonary sarcoidosis. Most of these patients had relapses after spontaneous improvement or initial response to treatment, showing either acutely-developed lesions in the periphery of the lung or

*From the Second Medical Department, Wilhelminenepital, Nuclear Medical Department, and Ludwig Boltzmanninstitute for Nuclear Medicine Wilhelminenepital, Vienna, Austria. Presented in part at the 9th International Conference on Sarcoidosis, Paris, August 1981. Manuscript received February 24; revision accepted June 18. Reprint requests: Dr. Kiech, 2nd Medical Department, Wilhelminenepital, Vienna, Austria A-1180

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deterioration of lung function and clinical symptoms, or extrapulmonary lesions.

Assessments

Chest X-Ray (Anteroposterior and Lateral): Evaluation has been performed by two independent observers using similar criteria of description: positive chest x-ray film (specified by progressive, stable, or regressive) or negative chest x-ray film (showing no specific abnormalities).

*67Ga Scanning: A whole body hybrid scanner (Scanner-camera, CGR; spectrometer setting 150 to 400 KEV) was used. Gallium imaging was done 72 hours after intravenous administration of 3 mCi of *67Ga citrate. Gallium uptake in lungs, hilar area, mediastinum, or extrapulmonary lesions was compared to activity in shoulder and liver using a scoring system varying from 0 to 3.

A score of 0 was defined when gallium uptake in areas of interest was less than activity in the shoulder. A score of 1 was given when activity proved to be less than in liver. Score of 2 was given in case of equal activity of liver, and 3 was defined when gallium uptake exceeded the activity in the liver (Fig 1 and 2). The evaluation of scoring was performed by two independent observers.

Angiotensin Converting I Enzyme Serum Assay (S-ACE): S-ACE activity in the serum was measured photometrically according the method of Cushman and Cheung, modified by Lieberman. The S-ACE activity was expressed in nanomoles hippuric acid liberated per minute at 37°C per milliliter serum (nmol/min/ml=U/ml). As normal range, S-ACE levels of a healthy control group (n=21) with a mean level of 13 ± 4.2 SD were used. Serum levels about 24 U/ml were regarded to be elevated.

T-Lymphocyte Subpopulations in Blood: T-lymphocytes were identified by their ability to form spontaneous rosettes at 4°C with neuraminidase-treated sheep red blood cells. A decrease of blood T-lymphocytes below 40 percent of total lymphocyte count (normal range of T-lymphocytes: 50 percent to 70 percent) was regarded as abnormal.
Table 1—Mean S-ACE Levels in Patients with Active and Inactive Sarcoidosis: Influence of Steroid Treatment

<table>
<thead>
<tr>
<th>S-ACE Levels</th>
<th>Without Cortisone Treatment</th>
<th>Cortisone Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} \pm SD )</td>
<td>( \bar{x} \pm SD )</td>
</tr>
<tr>
<td>Active Sarcoidosis</td>
<td>( 38.98 \pm 18.21 )</td>
<td>( 29.78 \pm 13.07 )</td>
</tr>
<tr>
<td>(n = 110)</td>
<td>(n = 86)</td>
<td>(n = 24)</td>
</tr>
<tr>
<td>Inactive Sarcoidosis</td>
<td>( 19.62 \pm 8.6 )</td>
<td>( 19.68 \pm 8.83 )</td>
</tr>
<tr>
<td>(n = 84)</td>
<td>(n = 60)</td>
<td>(n = 24)</td>
</tr>
</tbody>
</table>

* \( p < 0.001 \)

All assessments were to be performed during one week. Current steroid treatment was to be interrupted three days before taking blood samples or injection of \(^{67}\text{Ga} \) until time of scanning.

RESULTS

S-ACE Levels in Patients with Sarcoidosis

In the present study of patients with active sarcoidosis (n=35), S-ACE levels were significantly higher than in patients with inactive sarcoidosis (n=25) \( \bar{x} = 33.36 \text{ U/ml} \pm 14.11 \), and 17.7 U/ml \( \pm 6.26 \) respectively, \( p < 0.001 \).

Since 1978, we have used S-ACE assays for diagnosis and clinical management of patients with sarcoidosis. The results of 194 S-ACE assessments in patients with sarcoidosis are shown in Table 1. The S-ACE levels (n=86) in patients with proven active but untreated sarcoidosis were significantly higher \( (p < 0.001) \) than S-ACE levels (n = 60) in patients with inactive sarcoidosis \( (\bar{x} = 38.98 \text{ U/ml} \pm 18.21 \) and \( \bar{x} = 19.62 \text{ U/ml} \pm 8.6 \) respectively).

In patients who were treated with corticosteroids but showing still persisting signs of activity, the S-ACE levels \( (n = 24, \bar{x} = 29.78 \pm 13.07) \) were reduced in comparison to the levels in untreated patients with active sarcoidosis \( (p < 0.025) \).

However, in patients with current steroid treatment but with still persisting signs of activity, S-ACE levels \( (n = 24, \bar{x} = 19.68 \pm 8.83) \) of patients with inactive sarcoidosis with steroid treatment.

S-ACE and \(^{67}\text{Ga} \) Scanning

In patients with untreated sarcoidosis \( (n = 60) \), elevated S-ACE levels correlated significantly with the gallium score \( (r = 0.59, p < 0.001) \) (Fig 3).

Sensitivity of Different Parameters for Assessment of Activity

For the assessment of activity in patients with untreated active sarcoidosis \( (n = 35) \), \(^{67}\text{Ga} \) scanning showed the highest true positive ratio of 94 percent \( (= \text{sensitivity}) \) (Fig 4). X-ray films proved to be sensitive in 80 percent, followed by S-ACE levels with 77 percent sensitivity. A significant decrease of T-cell numbers in peripheral blood could only

![Figure 3. Correlation between S-ACE levels and \(^{67}\text{Ga} \) score in patients with biopsy proven sarcoidosis (n=60).](Image)

![Figure 4. Sensitivity of different parameters to assess activity in patients with active sarcoidosis (n=35).](Image)
be observed in 48 percent of patients with active sarcoidosis.

**Specificity of Different Parameters for Exclusion of Activity**

In patients (n = 25) with inactive sarcoidosis, S-ACE levels gave correct negative results in 88 percent (= specificity) (Fig 5). In spite of its high sensitivity, 67Ga scanning showed a low specificity and gave correct negative results only in 68 percent of inactive sarcoidosis. The specificity of chest x-ray films could not be established since a normal chest film was one of the criteria to define inactive sarcoidosis.

![Figure 5](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21326/)  
**Figure 5.** Specificity of different parameters for exclusion of activity in patients with inactive pulmonary sarcoidosis (n=25).

![Figure 6](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21326/)  
**Figure 6.** Sensitivity of different parameters for assessment of activity in patients with different types of active sarcoidosis (n=35).

### Table 2—Mean S-ACE Levels and Mean 67Ga Score in Patients with Different Types of Active Sarcoidosis

<table>
<thead>
<tr>
<th>Active Sarcoidosis</th>
<th>Active Sarcoidosis</th>
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<tbody>
<tr>
<td>radiographic type I (n = 13)</td>
<td>radiographic type II or III or extrapulmonary sarcoidosis (n = 22)</td>
</tr>
<tr>
<td>S-ACE (U/ml)</td>
<td></td>
</tr>
<tr>
<td>x ± SD</td>
<td></td>
</tr>
<tr>
<td>39.03 ± 16.6</td>
<td>28.99 ± 12.45*</td>
</tr>
<tr>
<td>67Ga Score</td>
<td></td>
</tr>
<tr>
<td>x ± SD</td>
<td></td>
</tr>
<tr>
<td>2.35 ± 0.52</td>
<td>1.52 ± 0.89†</td>
</tr>
</tbody>
</table>
| *p < 0.05  
| †p < 0.005 |

**Sensitivity of Parameters for Assessment of Activity in Different Types of Active Sarcoidosis**

To evaluate differences between various types of active sarcoidosis, these patients (n = 35) have been divided into two groups (Fig 6):

1. **Patients with only bihilar lymph node involvement (n = 13).** All parameters except T-lymphocyte decrease gave high positive results and showed a sensitivity of nearly 100 percent. In this group of patients, a strong positive correlation between x-ray and 67Ga scanning for detection and evaluation of bihilar lymph node enlargement could be observed.

2. **Patients with lesions in the periphery of the lung or extrapulmonary sarcoidosis (n = 22):** Chest x-ray film observation failed to document activity in seven of 22 patients (sensitivity only 68 percent). In this group, 67Ga scanning with a sensitivity of 91 percent proved to be the most sensitive parameter.
Assessment of Activity in Sarcoidosis

The main issue in clinical management of sarcoidosis is the evaluation and grading of the disease activity, which has to be defined very specifically and used as a clinical term leading to possible therapeutic decisions. However, in monitoring therapy and long-term control of patients with recurrent sarcoid-

S-ACE Levels and 67Ga Score in Different Types of Active Sarcoidosis

The mean value of S-ACE levels and 67Ga scores in the first group of patients with only hilar lymph node enlargement proved to be significantly higher than in patients with other presentations of active sarcoidosis (p < 0.005, p < 0.05) (Table 2).

Value of S-ACE and 67Ga Scan for Monitoring the Clinical Course of Patients with Sarcoidosis

In follow-up investigations of patients with sarcoidosis, S-ACE levels and 67Ga score were able to reflect the clinical activity of the disease. In some cases, S-ACE levels and 67Ga scanning proved to be more sensitive than chest x-ray film observations for early detection of relapses, as well as for evaluating the effect of therapy. Examples are given in Figures 7 and 8.

Discussion

Diagnosis of sarcoidosis is based on clinical and immunologic features together with histologic proof of sarcoid granuloma which mostly will be obtained by invasive means such as mediastinoscopy, transbronchial needle biopsy during bronchoscopy, and liver, skin, and other tissue biopsies. The main issue in clinical management of sarcoidosis is the evaluation and grading of the disease activity, which has to be defined very specifically and used as a clinical term leading to possible therapeutic decisions. However, in monitoring therapy and long-term control of patients with recurrent sarcoid-

Figure 7. Eleven month observation of patient with sarcoidosis showing recurrent activity. In April 1981, chest x-ray film failed to assess activity, whereas S-ACE levels and 67Ga scanning gave adequate information.

Figure 8. A 21-month observation of patient with sarcoidosis showing recurrent activity. In January 1981, in spite of low-dose steroid treatment, relapse was observed assessed by elevated S-ACE levels, increased gallium uptake, and definite clinical symptoms, whereas chest x-ray film failed to assess activity.
osis, the assessment of activity, if possible, should be restricted to noninvasive methods, excluding recurrent tissue biopsies.

It was the aim of this study to examine practical and clinical implications regarding the value of some recently developed means to assess activity of sarcoidosis compared to classic investigations such as chest roentgenography.

**S-ACE Levels**

In a three-year follow-up study in patients with sarcoidosis, the known relationship between elevated S-ACE levels according to the activity of sarcoidosis and the influence of steroid treatment\(^\text{18}\) was confirmed.

Since the mechanism of the change of angiotensin converting enzyme in active sarcoidosis is not yet known, involved lymph nodes with granuloma formation have been suspected to be the source of the increase.\(^\text{19}\) These findings seem confirmed by this present study, since in the group of patients with active sarcoidosis characterized by bilar lymph node enlargement, the determination of S-ACE levels was a more sensitive marker of activity and showed significantly higher mean levels than in other groups with peripheral and interstitial lesions of the lung.

**\(^\text{67}^{\text{Ga}}\) Scanning**

\(^\text{67}^{\text{Ga}}\) Gallium scanning has been described as a very sensitive method for detecting granuloma formation in sarcoidosis.\(^\text{8,10}\) Due to the mechanism of \(^\text{67}^{\text{Ga}}\) uptake in the tissue,\(^\text{20}\) gallium scanning is predicted to be a valuable but rather nonspecific supplement for diagnosis of sarcoidosis. In this study in terms of assessment of activity, \(^\text{67}^{\text{Ga}}\) scanning proved to be the most sensitive tool of all examined factors. This seems of particular value in advanced cases of sarcoidosis (mostly radiologic type II or III) where only \(^\text{67}^{\text{Ga}}\) scanning showed a sensitivity of over 90 percent followed by S-ACE (72 percent) and chest x-ray film (68 percent). However, a higher mean \(^\text{67}^{\text{Ga}}\) uptake could be found in patients with bilar lymph node enlargement. This phenomenon can be possibly explained by the extensive accumulation of the isotope in the granuloma mass of the bilar lymph nodes. Gallium scanning is able to show even small units of involved tissue such as lacrimal and salivary glands. The disadvantage of \(^\text{67}^{\text{Ga}}\) scanning is its low specificity.

In accordance with Gupta et al.,\(^\text{6}\) a statistical significant correlation \((r = 0.59, p < 0.001)\) between \(^\text{67}^{\text{Ga}}\) score and S-ACE levels was found.

In this study, \(^\text{67}^{\text{Ga}}\) scanning proved to be a valuable means in monitoring both the activity and extent of sarcoidosis and was helpful for adequate control of therapy showing a very close accordance with the clinical course and picture of the disease. However, the radiation exposure is a limiting factor for extensive use of this method. If gallium is administered during concomitant steroid therapy, the value of scanning is doubtful because of possibly suppressed \(^\text{67}^{\text{Ga}}\) uptake in the granuloma tissue.\(^\text{6}\) In this study, current steroid therapy was interrupted three days before administering \(^\text{67}^{\text{Ga}}\) to avoid the suppression of \(^\text{67}^{\text{Ga}}\) uptake.

**Chest X-Ray Examination**

In clinical practice, chest x-ray films are, in most cases, the first indicator for the diagnosis of sarcoidosis. The classic staging of sarcoidosis is based on roentgenographic features. Some discrepancies between serial chest x-ray observations and the clinical course of patients with sarcoidosis raised doubts about the value of staging of lung involvement in sarcoidosis according to findings on a chest roentgenogram. These discrepant experiences are partly substantiated by recent reports comparing bronchoalveolar lavage or gallium scanning with chest x-ray film findings.\(^\text{8,10,21}\)

In our experience in patients with interstitial involvement of the lung, mostly individuals who relapsed with various degrees of fibrotic residua, chest x-ray films failed to document activity in about one third of the cases.\(^\text{6}\) Gallium scanning and S-ACE levels gave markedly better results in this group of patients.

The value of the assessment of blood T-lymphocytes in this study remained inconclusive, mainly because of small numbers of performed assays. However, recent studies suggest that assaying of T-lymphocytes together with identification of T-cell subtypes from bronchoalveolar lavage fluid reflects more closely the intensity of the granulomatous process in the lung, giving more consistent information about disease activity by measuring the degree of alveolitis.\(^\text{11,15-18,21,22}\)

The *Kveim test* is widely used as a helpful tool in diagnosis of sarcoidosis, which gives positive results in about 65 percent (range 44 percent to 85 percent) in patients with bilar sarcoidosis.\(^\text{19-26}\) However, in patients with pulmonary infiltrates only or patients with recurrent sarcoidosis, a granulomatous response has been found to occur only in a minority of those cases.\(^\text{26}\) According to these findings, and partly due to the problem of insufficient validation of available Kveim test suspensions, in this study a Kveim test has not been performed on a routine basis. In our experience over the last
ten years in patients with sarcoidosis, apart from the
case of Kveim testing for diagnosis of sarcoidosis,
the test was not able to contribute essentially either
to the assessment of activity in patients with
recurrent sarcoidosis or to the daily clinical manage-
ment of sarcoidosis, mainly because of the long
periods which are necessary to obtain reliable re-
results.

In conclusion, the results of the present study
raise the following clinical implications: Elevated
S-ACE levels together with a score of $^{67}$Ga scanning
are sensitive indicators of activity in sarcoidosis,
while serial chest x-ray observations alone are not
sufficient for adequate management and control of
patients with sarcoidosis, including monitoring of
therapy, and should be combined at least with
S-ACE level assays. Although the use of $^{67}$Ga scanning
is limited due to its radiation exposure, it is a
valuable supplement to chest roentgenography and
S-ACE levels, particularly for assessment of activity
in cases of pulmonary or extrapulmonary tissue
involvement, facilitating therapeutic decisions for
corticosteroid treatment (indication, proof of effi-
cacy, dosage adjustment, etc.), and diagnosis of
doubtful cases. Normal S-ACE levels together with
negative $^{67}$Ga scans give a high predictive value for
excluding active sarcoidosis.

ACKNOWLEDGMENT: We thank Mrs. E. Schön and
Mrs. J. Hartmeyer M.D., for helpful assistance.

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