Correlative Analysis of Longitudinal Changes in Bronchoalveolar Lavage, \(^{67}\)Gallium Scanning, Serum Angiotensin-converting Enzyme Activity, Chest X-ray, and Pulmonary Function Tests in Pulmonary Sarcoidosis

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Despite the relatively high cost and complicated procedures, Gallium-67 (\(^{67}\)Ga) scanning and bronchoalveolar lavage (BAL) are increasingly advocated as more sensitive indicators of disease activity in sarcoidosis than chest X-ray and serum angiotensin-converting enzyme activity (SACE). To evaluate the clinical usefulness of \(^{67}\)Ga scanning and BAL, we followed 31 patients with pulmonary sarcoidosis, using these four parameters, at 9- to 24-month intervals over periods of 9 to 48 months. We obtained 68 complete evaluations. Close correlations were observed among chest X-ray, \(^{67}\)Ga scanning, SACE, and the percentage of lymphocytes in BAL fluid (p < 0.1 to 0.001). Longitudinal changes were also well correlated in these four parameters (p < 0.001) and paralleled the changes in vital capacity (p < 0.01 to 0.001). However, we were unable to predict the patients’ outcome from the initial evaluation of these four parameters. These results suggest that, in terms of their usefulness for estimating disease activity, the differences among these four indicators are negligible. We therefore conclude that chest X-ray and SACE sufficiently reflect disease activity and that, at present, routine evaluation by \(^{67}\)Ga scanning and BAL are not necessarily indicated in the long-term management of pulmonary sarcoidosis.

Key Words: Pulmonary sarcoidosis, Gallium-67 scanning, Bronchoalveolar lavage, Serum angiotensin converting enzyme, Chest X-ray, Pulmonary function test

Although pulmonary sarcoidosis is well known for its benign natural history, a minority of patients exhibit progressive lung disease. One of the major problems in managing patients with sarcoidosis is correctly estimating disease activity and making an accurate prognosis. Many investigators have attempted to establish correlations between the course of the disease and the results of several types of examination, including conventional chest X-ray, \(^{67}\)Ga scanning (SACE), and bronchoalveolar lavage (BAL). However, there have been numerous disputes concerning the clinical usefulness of each type of examination in evaluating patients with pulmonary sarcoidosis.

In this context, we designed a study to answer four questions: (1) Are there any correlations among the results obtained simultaneously from chest X-rays, \(^{67}\)Ga scans, SACE, and BAL? (2) Is it possible to predict the course of the disease on the basis of these four parameters? (3) Are there any correlations among the longitudinal changes revealed by these four parameters? (4) Which parameter is most appropriate and practical as an aid to the clinician in following the patient with sarcoidosis?

In attempting to answer these questions, we...
studied 31 patients with pulmonary sarcoidosis in whom it was possible to repeatedly and simultaneously obtain chest X-rays, $^{67}$Ga scans and SACE measurements and perform, BAL and pulmonary function tests. Each patient was examined two or more times at 9- to 24-month intervals for periods of up to 48 months.

**PATIENTS AND METHODS**

Study population: The patient population comprised 10 males and 21 females with a mean age of 39.1 ± 2.7 years. All patients had histologically confirmed pulmonary sarcoidosis. No patient received corticosteroid therapy during the 6 months before the initial evaluations. Fifteen patients received prednisolone during the study period because of cardiac dysrhythmia, severe opthalmologic involvement, or progressive lung disease. These 15 patients were re-evaluated 6 or more months after cessation of corticosteroid therapy to rule out the influence of the medication on the results of the examinations. Informed consent was obtained from all patients.

Chest X-ray: Standard high-kilovoltage postero-anterior films were obtained at maximal inspiration. The findings were classified as either negative, with no parenchymal infiltrates (by standard classification, type 0 or 1), or positive, with parenchymal infiltrates (type 2 or 3). The 31 patients were divided into two groups according to the longitudinal pattern of chest X-ray findings. Regardless of the initial findings, patients with negative chest X-rays at the last evaluation were placed in the "favorable" group and those with positive chest X-rays in the "persistent disease" group.

$^{67}$Ga scan: Each patient received 2 mCi of $^{67}$Ga-citrate intravenously 48 hours prior to scanning. Although both anterior and posterior rectilinear scans were recorded with a whole-body imager from head to abdomen, including the liver, only the posterior scans were used to estimate the degree of $^{67}$Ga uptake by the lung. For the latter evaluation, the grades of intensity were as follows: grade 0, equal to body background as determined from upper arm uptake; grade 1, equal to shoulder joint uptake; grade 2, intensity intermediate between grades 1 and 3; grade 3, uptake equal to greater than that of the liver.

To validate the normal $^{67}$Ga uptake by the lung, $^{67}$Ga scans from 30 control subjects with nonmalignant extrapulmonary disease and normal chest X-rays were also evaluated. At no time did any control subject show an uptake of grade 2 or more in the lung field. Accordingly, $^{67}$Ga lung scans were considered normal if the uptake was grade 1 or lower (negative $^{67}$Ga scan) and abnormal if the uptake was grade 2 or higher, which indicated uptake in at least one third of the lung field (positive $^{67}$Ga scan). Based on the final $^{67}$Ga scan results, the patients were placed in either the "favorable" or the "persistent disease" group.

Chest X-ray and $^{67}$Ga scans were interpreted blindly by the staff physician of the Department of Radiology.

SACE: SACE activity was determined by a modification of the spectrophotometric method of Cushman and Cheung which is based on the liberation of hippurate by ACE at pH 8.3, with hippuryl-L-histidyl-L-leucine used as the substrate. The concentration of sodium hippuric acid was measured with a spectrophotometer at 228 nm. The normal value for SACE in our laboratory is 40.3 ± 11.8 nmol/min/ml (mean ± SD). In this study, values of 64 nmol/min/ml (mean ± 2 SD of normal value) or higher were considered abnormal. The final SACE levels were used to assign the patients to the "favorable" group (SACE < 64 nmol/min/ml) or the "persistent disease" group (SACE ≥ 64).

BAL: In all patients, BAL was performed with 150 ml of sterile physiological saline in a segment or subsegment of the right upper anterior bronchus. The cell number was determined by hemocytometer counts of the BAL fluid. The morphologic characteristics of the recovered cells were determined form Wright-Giemsa-stained, cytocentrifuged cell monolayers, and the proportion of lymphocytes to total recovered cells (BAL lymph %) was calculated. Values of 35% or greater were considered high. Again, the patients were assigned to either the "favorable" group (BAL lymph < 35%) or the "persistent disease" group (BAL lymph ≥ 35%) on the basis of the final BAL results.

Scoring of the four parameters: The results of the four simultaneous evaluations were scored so
Table 1. Percentage of lymphocytes in BAL fluid and serum ACE activity

<table>
<thead>
<tr>
<th>Finding of Chest X-ray or $^{67}$Ga Scan</th>
<th>n</th>
<th>Lymphocyte Percentage in BAL Fluid (%)</th>
<th>Serum ACE Activity (nmol/min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray (-)</td>
<td>41</td>
<td>22.2 ± 2.9*</td>
<td>54.2 ± 3.0**</td>
</tr>
<tr>
<td>Chest X-ray (+)</td>
<td>27</td>
<td>33.9 ± 3.2</td>
<td>84.0 ± 5.3</td>
</tr>
<tr>
<td>$^{67}$Ga scan (-)</td>
<td>41</td>
<td>23.4 ± 2.9</td>
<td>59.9 ± 4.1*</td>
</tr>
<tr>
<td>$^{67}$Ga scan (+)</td>
<td>27</td>
<td>32.5 ± 3.8</td>
<td>75.9 ± 5.3</td>
</tr>
</tbody>
</table>

*p<0.01, **p<0.005

Data analysis: Statistical significance was determined by two-tailed t test for paired and unpaired data. For comparison of chest X-rays and $^{67}$Ga scans, the chi-squared method was used, and a probability of $p<0.05$ was considered significant. All date are expressed as the mean ± SD unless otherwise indicated.

RESULTS

Correlations among chest X-ray, $^{67}$Ga scan, SACE, and BAL lymph: A total of 68 complete evaluations was made during a mean follow-up period of 25.6 ± 1.9 months. All data obtained from the 68 evaluations were analyzed (Table 1). Twenty-seven patients had both chest X-rays and $^{67}$Ga scans performed. The chi-squared ($X^2$) test for correlation was used, and a $p$ value of 0.05 was considered significant. The test was performed for each parameter and the combination of chest X-ray and $^{67}$Ga scan.

Table 2. Relationship between chest X-ray and $^{67}$Ga scan in 31 patients

<table>
<thead>
<tr>
<th>Chest X-ray</th>
<th>$^{67}$Ga scan (+)</th>
<th>68 Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>(-)</td>
<td>7</td>
<td>34</td>
</tr>
</tbody>
</table>

$X^2 = 17.94$, $p<0.001$

Table 3. Changes in lymphocyte percentage in BAL fluid and serum ACE activity during the study period

<table>
<thead>
<tr>
<th>Change of Parameter</th>
<th>n</th>
<th>Lymphocytes in BALF (%)</th>
<th>Serum ACE (nmol/min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Initial)</td>
<td>(Final)</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>20</td>
<td>31.6 ± 4.3 ——&gt; 12.9 ± 2.4*</td>
<td>73.2 ± 5.8 ——&gt; 47.9 ± 3.3*</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>11</td>
<td>39.2 ± 4.8 ——&gt; 37.9 ± 5.9</td>
<td>83.6 ± 8.7 ——&gt; 72.6 ± 7.6</td>
</tr>
<tr>
<td>$^{67}$Ga scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>16</td>
<td>30.7 ± 4.8 ——&gt; 12.8 ± 3.5*</td>
<td>71.5 ± 7.1 ——&gt; 46.3 ± 5.0*</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>15</td>
<td>38.1 ± 4.7 ——&gt; 30.6 ± 5.1</td>
<td>81.1 ± 6.8 ——&gt; 72.7 ± 8.5</td>
</tr>
<tr>
<td>Serum ACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>19</td>
<td>31.9 ± 4.0 ——&gt; 12.8 ± 3.5*</td>
<td></td>
</tr>
<tr>
<td>(Persistent)</td>
<td>12</td>
<td>39.0 ± 5.8 ——&gt; 36.8 ± 5.8</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001
positive chest X-ray evaluations were accompanied by significantly high values for BAL lymph (33.9 ± 3.2%) and SACE (84.0 ± 5.3 nmol/min/ml), as compared to the 41 negative chest X-ray evaluations (BAL lymph: 22.2 ± 2.9; SACE: 54.2 ± 3.0). A similar tendency was observed in terms of $^{67}$Ga uptake although the elevation in the BAL lymph value was not significant.

The chest X-ray and $^{67}$Ga data were significantly correlated as shown in Table 2. Of the 68 simultaneous evaluations, there were 54 (79%) in which the chest X-ray findings corresponded to those of $^{67}$Ga scans (chi square = 17.94, p < 0.001); that is, in 20 evaluations both the chest X-ray and $^{67}$Ga scan were positive and in 34 both were negative.

A significant correlation between SACE levels and BAL lymph was also observed (r = 0.58, p < 0.001; data not shown).

**Longitudinal correlations among chest X-ray, $^{67}$Ga scan, SACE and BAL lymph (Table 3):** In 20 patients in the favorable group for chest X-ray, the mean value for BAL lymph at the initial evaluation was 31.6 ± 4.3%, and this decreased to 12.9 ± 2.4% at the final evaluation (p < 0.001). The mean value for SACE in this group also decreased, from 73.2 ± 5.8 nmol/min/ml (initial test) to 47.9 ± 3.3 (final test) (p < 0.001). On the other hand, in 11 patients in the persistent disease group for chest X-ray, the average values for BAL lymph and SACE remained high: 39.2 ± 4.8% (initial) to 37.5 ± 5.9% (final) and 83.6 ± 8.7 nmol/min/ml (initial) to 72.6 ± 7.6 (final), respectively.

A similar correlation was noted between the longitudinal changes in $^{67}$Ga scans and those of both BAL lymph and SACE. Namely, significant decreases in BAL lymph and SACE occurred in 16 patients in the favorable $^{67}$Ga scan group, while these parameters remained high in 15 patients with persistent disease according to $^{67}$Ga scans.

A significant decrease in BAL lymph was also observed in the 19 patients in the favorable group for SACE (p < 0.001), whereas in the 12 patients in the persistent disease group BAL lymph remained high.

Changes in chest X-ray findings were also well correlated with those in $^{67}$Ga scans in 25 of the 31 patients (81%). Fifteen patients were favorable for both, and 10 were persistent for both (chi square = 9.85, p < 0.005; data not shown).

**Correlations between pulmonary function and chest X-ray, $^{67}$Ga scan, SACE, and BAL lymph findings:** Table 4 shows the changes, in %VC and %DLCO with the patients divided into two groups according to the changes in the other four parameters. In the 20 patients in the favorable group for chest X-ray, the mean %VC increased from 108.3 ± 3.6% at the initial evaluation to 117.8 ± 3.8% (p < 0.001). On the other hand, in the 11 patients in the persistent disease group for chest X-ray, average %VC did not

Table 4. Changes in percent vital capacity (%VC) and percent diffusing capacity (%DLCO) according to changes in findings of chest X-ray, $^{67}$Ga scan, serum ACE activity, and lymphocyte percentage in BAL fluid (BAL lymph)

<table>
<thead>
<tr>
<th>Change of Parameter</th>
<th>n</th>
<th>%VC (Initial)</th>
<th>%VC (Final)</th>
<th>%DLCO (Initial)</th>
<th>%DLCO (Final)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>20</td>
<td>108.3±3.6</td>
<td>117.8±3.8**</td>
<td>86.0±5.2</td>
<td>83.1±4.8</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>11</td>
<td>100.9±4.7</td>
<td>101.9±6.8</td>
<td>96.1±7.8</td>
<td>93.5±11.6</td>
</tr>
<tr>
<td><strong>$^{67}$Ga scan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>16</td>
<td>110.0±3.7</td>
<td>117.4±5.4*</td>
<td>91.6±6.3</td>
<td>93.9±7.2</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>15</td>
<td>101.8±4.1</td>
<td>107.2±4.8</td>
<td>87.8±5.9</td>
<td>81.8±6.9</td>
</tr>
<tr>
<td><strong>Serum ACE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>19</td>
<td>108.7±4.2</td>
<td>117.6±4.5**</td>
<td>90.2±5.6</td>
<td>84.6±5.3</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>12</td>
<td>101.0±3.8</td>
<td>102.8±5.8</td>
<td>89.2±7.0</td>
<td>91.4±10.0</td>
</tr>
<tr>
<td><strong>BAL Lymph</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Favorable)</td>
<td>21</td>
<td>107.0±3.8</td>
<td>116.5±4.2**</td>
<td>89.1±5.2</td>
<td>86.0±4.8</td>
</tr>
<tr>
<td>(Persistent)</td>
<td>10</td>
<td>103.3±4.5</td>
<td>104.0±6.7</td>
<td>91.2±7.9</td>
<td>92.6±12.4</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001
Table 5. Distribution of scores at the initial evaluation in 31 patients

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFT (↓)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>PFT (↑)</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>31</td>
</tr>
</tbody>
</table>

Nine patients functionally deteriorated (PFT (↓)) and 22 were functionally unchanged or improved (PFT (↑)) during the study period. PFT: pulmonary function test.

change significantly (100.9 ± 4.7% initially to 101.9 ± 6.8% at the final evaluation). The same was true for the changes in $^{67}$Ga scans, SACE, and BAL lymph values. That is, significant increases in the mean %VC occurred in the favorable groups whereas no significant changes in the %VC were observed in the persistent disease groups for each parameter.

However, as Table 4 shows, the changes in the %DLoCo were not correlated with any of the findings in the other four parameters. **Correlation of the score at initial evaluation with the outcome of pulmonary function:** To investigate the possibility of predicting long-term pulmonary function on the basis of the results of the four examinations, we compared the total scores for those examinations with the changes in PFT. Our findings are shown in Table 5. Of the 31 patients, 9 functionally deteriorated (PFT ↓) and 22 improved or were functionally unchanged (PFT ↑) during the study period. It is clear that the scores do not reflect the course of disease in terms of pulmonary function.

**DISCUSSION**

Many trials have been conducted concerning the estimation of disease activity, natural history, response to therapy, and prognosis in patients with pulmonary sarcoidosis. Various types of assessments have been studied, including chest X-ray, $^{67}$Ga scanning, SACE measurement, BAL, and pulmonary function tests.

Deremee reviewed the chest X-ray staging of sarcoidosis and emphasized that this approach is still uniquely valuable to the clinician in the classification of sarcoidosis and delineation of its clinical course and prognosis. However, Crystal and his colleagues refuted this assertion, claiming that chest X-ray findings are not adequate for predicting the course and prognosis of the disease.

As for SACE, its usefulness has been disputed as well. Numerous reports have extolled the usefulness of BAL and $^{67}$Ga scanning in evaluating the status and course of pulmonary sarcoidosis. The study by Keogh et al. has attracted particular attention. They emphasized that the "intensity of alveolitis" determined by the population of lung T-lymphocytes recovered by BAL, together with the results of $^{67}$Ga scanning, provided the best correlation, with the natural course and prognosis of the disease. However, the problems of high cost and the amount of radiation exposure have been pointed out. Moreover, controversy continues regarding the clinical usefulness of both BAL and $^{67}$Ga scanning.

Finally, long-term evaluations of the usefulness of these two tests in combination have been insufficient to allow definite conclusions to be reached.

Therefore, we followed 31 patients with sarcoidosis for a long period (25.6 ± 1.9 months) and examined the value of chest X-ray, $^{67}$Ga scanning, SACE measurement, BAL, as well as pulmonary function tests in determining disease activity and making prognoses. We administered the test simultaneously at intervals and assessed their usefulness and reliability both individually and in various combinations.

Our analysis of 68 simultaneous evaluations revealed that the four parameters employed were well correlated with each other, as shown in Fig. 1, although the correlation between the results of $^{67}$Ga scanning and BAL lymph was not statistically significant (p < 0.1). However, these four parameters are thought to reflect different pathophysiologic aspects of pulmonary sarcoidosis; therefore, synthetic analysis of the results is perhaps
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necessary to evaluate the disease activity.

In an initial attempt at synthetic analysis, we obtained an initial combined score, which was compared with the changes that occurred in pulmonary function. However, it was difficult to estimate the functional outcome from the results of either individual or combined laboratory examinations. We conclude that there are, at present, no known parameters that enable the clinician to make an accurate prognosis in cases of pulmonary sarcoidosis. However, more detailed methods of analyses of lymphocytes in BAL fluid and computer-analyzed qualitative $^{67}$Ga scans may become available in the future.

At present, the main clinical value of these parameters is in determining changes in the disease course through serial examinations, by comparing the results obtained from an individual patient over time. Although, in following patients with pulmonary sarcoidosis, it is desirable to examine multiple parameters, routine repetition of all four types of tests is too invasive and expensive for practical use. We therefore attempted to determine which parameters are most practical and useful in this respect.

We found that the longitudinal changes in the four parameters were well correlated with each other, as shown in Fig. 2. For instance, over the long-term the SACE and BAL lymph normalized in most patients in the group "favorable" for chest X-rays. The same was true for the patients in the "favorable" group for $^{67}$Ga scans. On the other hand, the values for SACE and BAL lymph were high in most patients placed in the "persistent disease" groups on the basis of chest X-rays and $^{67}$Ga scans. There were also significant correlations between the changes in chest X-rays and $^{67}$Ga scans and those in SACE and BAL lymph, respectively.

In addition, the changes in these four parameters paralleled the changes in vital capacity, although no parameter was correlated with the changes in diffusing capacity.

These results suggest that there are little differences in usefulness among these four parameters when patients with pulmonary sarcoidosis are followed over a long-term period. It is likely that chest X-ray and SACE are by no means inferior to $^{67}$Ga scanning and BAL in following and evaluating such patients. While there was a time lag in the changes that occurred in these parameters, we were unable to demonstrate that any single parameter was more sensitive or changed earlier in the evolution of pulmonary sarcoidosis. It is possible that changes in $^{67}$Ga scans and BAL lymph occur before those of chest X-rays and SACE measurements. However, the time lag does not seem to be clinically significant in terms of estimating the disease course and prognosis, since pulmonary sarcoidosis is almost always chronic and the opportunity for treatment may not be lost if chest X-rays and SACE measurements are obtained at 2- or 3-month intervals.

Thus, in clinical practice the following strategy is likely to be the most cost-effective and practical. First, a patient with pulmonary sarcoidosis should be evaluated on the basis of both chest X-ray and SACE measurement every 2 or 3 months, together with routine history-taking and physical examinations. Second, if there is any indication of progressive deterioration or intractability, serial pulmonary function tests should also be performed. Third, if pulmonary function deteriorates progressively over 6 to 12 months, corticosteroid therapy should be considered.

Actually, 14 of the 15 patients who required treatment with a corticosteroi because of progressive lung disease, cardiac dysrhythmia, or severe ophthalmologic involvement during the study period had abnormalities in their chest X-rays (parenchymal infiltrates) and/or SACE levels just before or at the time of treatment. The remaining patient, treated with a corticosteroid because of severe ophthalmologic involvement, has no abnormal findings in any of the four parameters. These results also support the contention that, in clinical practice, chest X-ray and SACE are sufficient parameters for following patients with sarcoidosis. It is obvious that routine electrocardio-
graphic and ophthalmologic examinations are also necessary in patients with cardiac and/or ophthalmologic involvement.

In conclusion, we consider that the results of chest X-ray and SACE are sufficient indicators, and that routine BAL and $^{67}$Ga scanning are not necessarily mandatory, in following and evaluating patients with pulmonary sarcoidosis. Our rationale is as follows: (1) The long-term functional outcome could not be predicted from analysis of the four parameters examined; (2) The changes in these parameters over a long-term period were well correlated with each other; (3) The changes in these parameters paralleled the changes in vital capacity; and (4) BAL and $^{67}$Ga scanning are much more expensive and invasive than are chest X-rays and SACE measurements.

ACKNOWLEDGEMENT: We are grateful to Dr. K. Ohara, Assistant Professor in the Department of Ophthalmology, Jichi Medical School, for his helpful suggestions regarding the diagnosis and treatment of the ophthalmologic lesion in these patients.

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