Clinical Conference

Sarcoidosis*
Usual and Unusual Manifestations

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Case Report

A 48-year-old black woman presented to the University Hospital Medical Center in 1978 with skin lesions. A chest radiograph obtained in 1970 was essentially normal. In March of 1978, she developed small nodules in both lungs and fullness in both hila. Bed rest and various creams for the skin lesions were prescribed. In November of 1978 she developed diffuse bilateral infiltrates and hilar adenopathy (Fig 1). A skin biopsy showed noncaseating granulomas. The patient was treated with prednisone for symptoms of cough, shortness of breath, arthralgias, and skin rash. Over the next five months her chest x-ray films showed improvement, and she was gradually taken off her steroid regimen. By 1981, her chest roentgenogram showed no evidence of lung disease, and her pulmonary function tests had returned to normal.

She initially came to our pulmonary clinic with absolutely no symptoms. Approximately one year later she returned with cough and shortness of breath. A chest roentgenogram showed new hilar adenopathy and a reticular nodular infiltrate. In addition to the worsening indicated by her chest film, her vital capacity had dropped to 2.2 L, one year earlier it had been 3.0 L. A gallium scan was positive in both lungs and both hila. A bronchoscopy with bronchoalveolar lavage showed a marked increase in the lymphocyte count to 63 percent of the cells retrieved by lavage. Normally, macrophages make up 90 to 95 percent of the cells retrieved by lavage and lymphocytes between 5 and 10 percent. Her CD4:CD8 ratio, determined on the lymphocytes from the lavage (CD4 for the helper cell, CD8 the suppressor cytotoxic cells) was 18. Serum calcium level was 11.1 mg/dl. She had new-onset anemia and new skin lesions on her legs. The angiotensin-converting enzyme (ACE) level was 60 units. The upper limit of normal for the age and sex of this patient is 35. All of these findings suggested active sarcoidosis, and she was started on steroid therapy. Her chest radiograph over the next two months showed marked improvement. Her vital capacity increased by 800 ml. Her other symptoms also resolved, and she never had further hypercalcemia. In 1985 she was off steroids and came every six months for routine follow-up. Her only problem at that time was osteoarthritis.

She came to see me in February 1987 with acute itching. She was obviously jaundiced and had an enlarged, tender liver. She had had no contact with anyone with known hepatitis, no recent blood transfusion, and was not an IV drug abuser. Hepatitis B antigen was found in her blood, and it was assumed she had acute hepatitis B. She was treated with antihistamines, which alleviated her itching somewhat. Over the next six weeks her transaminase and bilirubin levels continued to rise. Repeat studies of her hepatitis profile showed no further hepatitis B antigen. Because she never developed hepatitis B antibodies, it was thought that she had a false positive hepatitis B antigen rather than true hepatitis B. She was hospitalized for further evaluation.

At that time her alkaline phosphatase level was greater than 2,000 U, her bilirubin greater than 20 mg/dl, and her transaminases greater than 1,000 U. A hepatic imino diacetic acid (HIDA) scan did not show her ducts (Fig 2A); a transhepatic cholangiogram showed markedly dilated ducts. A computed axial tomography (CAT) scan suggested a lesion in the porta hepatis, thought to be most consistent with a cholangiocarcinoma. Exploratory laparotomy revealed grossly enlarged nodes at the porta hepatis, the probable

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Figure 1. Chest roentgenogram of patient in 1978, at time of original disease.
cause of the obstructive jaundice. Multiple biopsies of these nodes showed noncaseating granulomas; there was no evidence of tumor. A liver biopsy revealed both sarcoid granulomas and cholecystic changes.

A cholecystostomy tube was inserted for drainage. Postoperatively, her bilirubin leveled off at around 4 mg/dl and she was given high doses of steroids. Within two weeks, the bilirubin level fell to 1.3 mg/dl. A repeat HIDA scan showed a well-functioning liver and a normal common bile duct (Fig 2B).

Approximately two weeks after discharge, she was brought to the emergency room with focal seizures. Her admission serum glucose was 1,400 mg/dl, and she was given insulin to control her blood sugar. A CAT scan of the head showed no evidence of lesion.

Another two weeks after discharge, she experienced lightheadedness and dizziness, which I ascribed to hypoglycemic episodes. However, on checking her blood count, I found that her hematocrit had fallen from 40 to 14 percent. Gastroduodenal endoscopy revealed diffuse gastritis. Since prednisone did not seem to be effective, except for the sarcoidosis itself, she was switched to methotrexate therapy. Currently she takes 5 mg of prednisone every other day and 10 mg of methotrexate orally once a week. Her latest bilirubin level was 0.4 µg/dl.

Fortunately, this is not a typical case of sarcoidosis. This patient had several manifestations that are particularly interesting. She had disease over a ten-year period. She had lung and skin involvement, hypercalcemia, anemia, and liver involvement.

DISCUSSION

This article will discuss a common problem in sarcoidosis—lung involvement—and also some of the underrecognized associated problems, such as anemia, other leukopenias, and liver involvement. The final section discusses treatment, especially new forms of therapy.

Lung Involvement

Sarcoidosis is characterized by noncaseating granulomas in two or more organs. Its diagnosis is one of exclusion. Routinely, specimens must be cultured for fungi and tuberculous organisms because they can cause noncaseating granulomas.

The diagnosis of sarcoidosis is usually confirmed by the presence of one or more noncaseating granulomas in sites where granulomas usually caseate, such as the lung or the mediastinal lymph nodes. The liver and skin can form noncaseating granulomas to a wide variety of antigens, so diagnosis on the basis of liver or skin biopsy is usually subject to question.

The striking feature of the sarcoid granuloma is the large multinucleated giant cells surrounded by an influx of small mononuclear cells, most of which are lymphocytes. Immunohistochemical staining demonstrates that these lymphocytes surrounding the granuloma are T-helper cells (CD4+). A large amount of research is aimed at discovering how the sarcoid granuloma is formed. For whatever reason, the macrophage and T-cell interaction leads to the release of several lymphokines and monokines—including interleukin 1, gamma interferon, and interleukin 2—causing local proliferation, influx of monocytes and lymphocytes from the peripheral blood into the damaged area and eventual formation of a granuloma.

There are many disease activity indicators in sarcoidosis (Table 1). The erythrocyte sedimentation rate is a nonspecific marker of inflammation. Elevation in serum ACE, originally described in 1975, is seen in 60 to 80 percent of patients with active disease. There were great hopes for ACE as a marker for response to therapy. However, several studies suggested that steroids themselves affect ACE independently of the effect on the disease, and its elevation is really not as useful an indicator as originally thought. These two

Table 1—Proposed Markers of Disease Activity in Sarcoidosis

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Erythrocyte sedimentation rate</th>
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<tbody>
<tr>
<td></td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td></td>
<td>Pulmonary function tests</td>
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<tr>
<td></td>
<td>Vital capacity</td>
</tr>
<tr>
<td></td>
<td>Dco</td>
</tr>
<tr>
<td></td>
<td>Chest roentgenogram</td>
</tr>
<tr>
<td></td>
<td>Gallium scan</td>
</tr>
<tr>
<td></td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td></td>
<td>Percent lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte subpopulation</td>
</tr>
</tbody>
</table>

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tests are easy to obtain sequentially, since they only require a simple blood test.

Chest roentgenograms and pulmonary function tests are not good predictors of disease inflammation but are really representative of what has happened to the body. Changes in the chest x-ray film often show the end result, rather than what we are trying to predict. Likewise, changes in pulmonary function tests, including reduction of the Dco, only give information about the level of pulmonary insufficiency. Sometimes deterioration indicated by these tests is reversible, other times irreversible.

Bronchoalveolar lavage, on the other hand, is a fairly specific test for the increase in lymphocytes, especially in T-helper lymphocytes, seen in this disease. In patients who do not have sarcoidosis, bronchoalveolar lavage shows that 85 to 90 percent of the cells are macrophages, while lymphocytes and neutrophils make up less than 10 percent and 1 percent, respectively. In patients who smoke there is a slight increase in the amount of neutrophils, about three to four times that in nonsmokers. In patients with sarcoidosis, an increase in the number of lymphocytes seems to be even greater in people with more disease activity. In addition, the lymphocyte subpopulation ratio (CD4:CD8) increases. In normal subjects the lymphocyte subpopulation ratio in the lavage fluid is very similar to that in the blood (Fig 3). Patients with acquired immunodeficiency syndrome (AIDS) or hypersensitivity pneumonitis, have a marked reversal of the ratio, which is less than 1 and often less than 0.6. In patients with sarcoidosis, the opposite is true. In addition, the ratios are higher during active disease and normalize as the disease resolves. In distinguishing hypersensitivity pneumonitis from sarcoidosis, the use of murine monoclonal antibodies to identify subpopulations of the lavage can be useful, since patients with sarcoidosis tend to have high ratios (>2.0), while those with hypersensitivity pneumonitis have low ratios (<0.6). In infectious granulomatous diseases such as tuberculosis and in fungal infections, the ratio can be low, extremely low, or high.

Research has shown that the T-helper cells are increased in the lung and that they are quite active. Elegant studies by Crystal's group at the National Institutes of Health showed that these T-helpers secrete interleukin 2 in increased amounts. Interleukin 2 is an important lymphokine in the activation of other T-lymphocytes and the formation of granulomas. In the lavage fluid of patients with stable disease versus active disease, the CD4 lymphocytes of the active patients spontaneously secreted interleukin 2, while lymphocytes from the stable patients did not. Further studies showed that steroid therapy resulted in lymphocytes retrieved by lavage that no longer secreted interleukin 2. Lymphocyte function changed with steroid therapy, but lymphocyte number did not.

Although bronchoalveolar lavage provides important information regarding local response, it samples only a small portion of the lung. The gallium scan provides a measurement of the whole lung.

The gallium scan appears to be quite a sensitive indicator of active pulmonary sarcoidosis. It is very unlikely that patients with active sarcoidosis would have a negative gallium scan unless they were on steroid therapy. The test is, unfortunately, not specific, an accumulation of gallium in the lung can be seen in some patients with malignancy, pneumonia, or cryptogenic pulmonary fibrosis.

Why patients with active sarcoidosis have a positive gallium scan is not clear, but it seems to be due to activation of the macrophage; the gallium accumulates in the macrophages themselves. Patients with sarcoidosis can have diffuse or fairly localized gallium uptake. In either case, the percentage of gallium uptake in the lung can reflect the total amount of inflammation, very much like a sedimentation rate test of the lung.

Bronchoalveolar lavage, gallium scan, and ACE levels have been proposed as useful in predicting disease activity and identifying which patients will have significant progressive disease. A study at the National Institutes of Health on 19 patients not treated with steroids found that patients with positive gallium scans and positive lavage findings tended to deteriorate over the next six months. Unfortunately, most symptomatic sarcoidosis patients are treated with steroids. The relevant question for most clinicians is: How much better is someone going to get if given prednisone? In a study done at this institution of patients evaluated before and after two months of prednisone therapy, we compared the efficacy of ACE, gallium scan, and lavage findings in predicting the response of forced vital capacity to therapy. There was a wide range of the ACE levels before therapy, from normal to three times normal. Some patients with high ACE levels had greatly improved vital capacity; however,
there were also patients with nearly normal ACE levels who had even greater improvement. When we considered the amount of gallium uptake in relation to improvement, we found good correlation between the total gallium uptake and the degree of improvement there would be during steroid therapy. When we looked at the lymphocyte count in the lavage fluid, we found once again a very widespread scatter. Some patients with a very large percentage of lymphocytes in the fluid had very little improvement, while others with low lymphocytes had good improvement. Part of this may be due to the fact that, as patients are treated or improve spontaneously, they normalize the ratio of helper to suppressor cells but may still have an increased percentage of lymphocytes.\(^5,6\) The larger the number of CD4 lymphocytes in the lavage fluid, the better the improvement in vital capacity.

To date, there have been three published studies on the short-term response to steroid therapy.\(^6,7,8\) They have followed patients only for up to 22 weeks after therapy. The ACE level did not predict response to therapy in any of the studies. Some researchers, especially our group, have found gallium scans quite useful in predicting patients who would improve, while other groups have not been able to reproduce the utility of gallium scans. Part of this problem may be technical, since gallium scans can be read either as positive or negative, or one can choose a semiquantitative method. All groups have data suggesting that an increased number of CD4 lymphocytes may be useful markers in short-term response to therapy.

Whether any test has long-term prognostic value is a different question. The patient in this article, for example, had abnormal lavage results in 1982. She did well, and we expected her disease not to come back. Some patients continue to have disease, however, and it would be useful to be able to identify them. This has been studied by Neville et al, in London, where they looked at 818 patients, defined those who had disease for more than two years as chronic and those who had disease for less than two years as acute, and examined the factors associated with chronic disease.\(^19\) Some striking manifestations were associated with chronic disease. For example, of patients with evidence of cardiac involvement from sarcoidosis—a small number of patients—none had resolution of either their sarcoidosis or improvement of their chest x-ray films over a two-year period. Of those with lupus pernio, the relatively distinctive markings along the face, only seven of 24 had improved chest films, and only five had sarcoidosis in remission after two years. On the other hand, patients with erythema nodosum or acute arthritis had a very good chance that their x-ray would improve and that their sarcoid would be in remission within the two years. Their likelihood of developing chronic disease was predicted to be small.

We were interested in whether the additional information from gallium scans or lavage would help in these clinical observations. We reviewed 44 patients who had undergone multiple studies and followed them two years after original evaluation to see which ones still had disease. All were symptomatic initially. Seventy percent had a positive gallium scan on initial evaluation; more than 60 percent had elevated ACE levels or increased lymphocytes in the lavage fluid. We found that we could identify a subpopulation not likely to

### Table 2—Predictive Values of Various Pretreatment Tests

<table>
<thead>
<tr>
<th>Pretreatment Results</th>
<th>Positive Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallium scan positive</td>
<td>0.68</td>
<td>1</td>
</tr>
<tr>
<td>ACE &gt; 40 units</td>
<td>0.55</td>
<td>0.77</td>
</tr>
<tr>
<td>BAL T lymphocytes (&gt;24%)</td>
<td>0.50</td>
<td>0.61</td>
</tr>
<tr>
<td>BAL T4/T8 &gt; 2.4</td>
<td>0.42</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Abbreviations: ACE = angiotensin-converting enzyme, BAL = bronchoalveolar lavage.

have disease (Table 2). For example, a patient with a negative gallium scan had a negative predictive value of one, meaning no patient with a negative gallium scan still had disease activity two years after evaluation. A normal ACE level, less than 40 U/ml, was also associated with a strong possibility of no disease after two years. Negative tests were fairly useful in predicting who would no longer have active disease. One difficulty in this study was that most patients studied had abnormalities reflected by one or the other tests before therapy. We continue to look for good predictors of disease response, both short-term and long-term.

### Hematologic Involvement

The less commonly discussed manifestations of sarcoidosis are the hematologic ones. The patient in this study had anemia—a hematocrit of 31 in 1982, when she had a relapse. She eventually underwent bone marrow examination, which revealed noncaseating granulomas. This case and others led to a hematologic evaluation of patients with sarcoidosis. We examined 75 patients at this institution to see how many were leukopenic, lymphopenic, and anemic (Table 3). Several abnormalities were noted. Lymphopenia was seen in over half the patients with active disease, and anemia was seen in approximately one third. In patients who were anemic, an aggressive attempt was made to obtain bone marrow specimens.\(^11\) We were successful in 17 cases, and granulomas were identified in seven. Some patients had other causes for their anemia, including iron deficiency, but, overall, granuloma was the most striking finding. Also striking was the fact that the anemia normalized in patients treated with prednisone. Only one patient in this group required transfusion because of her anemia; she had severe cor pulmonale and did much better at a level of 12 g/dl than she did at 8 g/dl. With steroid therapy, she no longer required transfusion.

The lymphocyte count in patients with sarcoidosis is markedly reduced, especially in those with active disease.

### Table 3—Summary of Hematologic Abnormalities in 75 Patients with Pulmonary Sarcoidosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number*</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>55</td>
</tr>
<tr>
<td>Monocytosis</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>21</td>
<td>28</td>
</tr>
</tbody>
</table>

*Some patients had more than one abnormality; only ten had no abnormality.

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Lymphopenia, seen in over half the patients, was associated with low CD4 lymphocyte count in the peripheral blood. CD4 lymphopenia is also common in patients with AIDS, where a cytotoxic virus kills the CD4 cells. This is another disease in which the CD4 lymphocyte count can be extremely low in the peripheral blood, sometimes less than 500/cu mm. We have found that CD4 lymphopenia is significantly associated with an increase in the number of CD4 lymphocytes in lavage fluid.16 We believe this is due to C4 lymphocyte sequestration from the blood into areas of active inflammation, usually the lung.

Liver Involvement

Another manifestation of sarcoidosis in this patient was liver involvement. Most sarcoidosis patients with hepatic involvement develop increased alkaline phosphatase levels and a cholestatic pattern.53 However, they usually do not develop significant jaundice. Table 4 shows survey results of 105 sarcoid patients who have had liver function tests at this institution. An elevated bilirubin level was occasionally seen, but an elevated alkaline phosphatase level occurred about twice as often. Moreover, when one considers only those with significant (>two times normal) elevation, the alkaline phosphatase level was the major abnormality. Of four patients with alkaline phosphatase levels four or more times greater than normal, none had jaundice except for the patient described here.

Jaundice in patients with sarcoidosis has been reported in two settings. One is a primary cholestatic pattern that can mimic primary biliary cirrhosis.44 Fewer than 30 cases have been reported in the English language literature. An even more uncommon manifestation is obstruction of the biliary duct. A patient was reported in 1978 with exactly the same presentation as the case described here.50 That patient’s jaundice also responded to steroid therapy with subsequent shrinkage of nodes. In patients with sarcoidosis, jaundice should be considered unusual enough to require further evaluation and testing and should not be assumed to be due to the sarcoidosis. On the other hand, elevations of alkaline phosphatase are common and probably do not warrant further evaluation.

Treatment

In general, the therapy for sarcoidosis has been steroids or nothing.27 This practice is based on a few small studies that showed patients with pulmonary sarcoidosis improved markedly with cortisone and then relapsed when the steroids were withdrawn. There are no good controlled studies showing any long-term value of prednisone; however, almost everyone agrees that prednisone should be given to a symptomatic patient with sarcoidosis, especially one with life-threatening complications.

There are occasional patients, such as this one, who cannot take steroids, who would like to get off steroids because of intractable side effects, or who have fairly localized disease for which other therapies might be appropriate. A large number of regimens have been suggested, including anti-
malarials, chlorambucil, azathioprine, cyclosporine A, radio-
therapy, and methotrexate. Some of these have a fairly good rationale, based on what we know about the pathophysiology of sarcoidosis. Some are used because they seem to work.

Antimalarials are used because patients treated with them who incidentally had sarcoidosis had improvement in their sarcoidosis; such improvement occurs in approximately one third of patients with skin sarcoidosis. It is a very benign regimen. Recently, some patients with hypercalcemia have been successfully treated with antimalarials.54 Skin lesions and hypercalcemia are very easily measurable disease markers, and treatment with antimalarials is easily assessed. It is harder to follow patients with pulmonary disease and thus more difficult to determine whether the antimalarial has been successful.

cyclosporine A causes the T-helper lymphocyte to become less responsive to interleukin 2. Therefore, the drug should be quite useful in a T-helper–mediated disease such as sarcoidosis. Interestingly, the reports to date have been very uninspiring; the data suggest that there has been at best a limited response to cyclosporine. This makes us go back and think again about what the primary cause of sarcoidosis is, and what is the role of the T-helper lymphocytes in this disease.

Radiotherapy has been used in selected cases, specifically for patients with CNS sarcoidosis.55 Because lymphocytes are exquisitely sensitive to radiotherapy, this is a useful regimen and can also be used for disease in other sites.

Chlorambucil, azathioprine, and methotrexate are all immunosuppressants to various degrees, and their major use has been as steroid-sparing agents in collagen vascular diseases. The largest published experience was described by Kataria,56 who used chlorambucil. To date, he has treated 21 patients with various degrees of success. He continues to have good success with the drug and has not seen any long-term side effects, such as malignancies. (Kataria, personal communication).

We recently became interested in methotrexate mainly because of its fairly good results in rheumatoid arthritis.57 The drug’s major advantage over other immunosuppressants is that it does not seem to be induce malignancy. This has great appeal for patients who are obviously going to be alive for many years after initial therapy. We have treated five patients to date with methotrexate. The reason for metho-
trexate in two of the cases was severe sarcoidosis, pulmonary hypertension, and advancing disease with steroid therapy. These patients were switched to methotrexate, have had their prednisone dosages reduced, and still have had improve-
ment in their vital capacity and general lung function. Two patients could not take prednisone, one because she became flagrantly psychotic, the other because she had intractable diabetes. Methotrexate resolved the target lesion in both these patients. The patient described here not only has been able to decrease the amount of steroids with no

Table 4—Liver Function Test Abnormalities in 105 Patients with Sarcoidosis

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. Patients with Abnormality</th>
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<tbody>
<tr>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>35</td>
</tr>
<tr>
<td>Serum transaminases</td>
<td>15</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>7</td>
</tr>
<tr>
<td>Elevated more than two times normal levels</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>12</td>
</tr>
<tr>
<td>Serum transaminases</td>
<td>3</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1</td>
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further complications of her diabetes or bleeding, but has also continued to show improvement in liver function, as assessed by serum bilirubin levels.

SUMMARY

The case presented here is not the typical picture of sarcoidosis. It is quite unusual for patients to have disease for so long with such extensive involvement of so many different organs. However, sarcoidosis can involve many organs, and one should be aware of that possibility. Sometimes the involvement can be very mild and may only be a clue to its underlying cause, such as anemia. Sometimes involvement can be specific and a distinct reason for treatment, such as hypercalcemia. Whatever the presentation, the disease must be monitored, and one must always remember that it can recur in unexpected ways, as it did in this patient.

Dr. Peter Walzer: I have a question about patients treated with steroids. Much of your data on treatment is based on the sarcoidosis population. Do you have comparable studies of patients with other diseases to whom steroids have been given and their T-lymphocyte studies follow sequentially?

Response: Are you talking about peripheral blood or lavage?

Dr. Walzer: Lavage.

Response: The only studies of T-lymphocytes in lavage other than in sarcoidosis have been in hypersensitivity pneumonitis. There, it is not a CD4 but a CD8 influx. Patients appear to normalize their ratio, with remission of their disease. Most other diseases with increased lymphocytes in the lavage fluid have a very unpredictable influx of helper and suppressor lymphocytes, probably showing how bad the current markers are. In sarcoidosis it works very nicely.

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