Lymphocytic Interstitial Pneumonia in Patients at Risk for the Acquired Immune Deficiency Syndrome

John C. Morris, M.D.;† Mark J. Rosen, M.D., F.C.C.P.;‡ Alberto Marchevsky, M.D.,§ and Alvin S. Teirstein, M.D., F.C.C.P.¶

Three patients with the acquired immune deficiency syndrome (AIDS) or AIDS-related complex and lymphocytic interstitial pneumonia are reported. All patients presented with progressive dyspnea, nonproductive cough, fever, anorexia, weight loss, and arterial hypoxemia. Chest roentgenograms exhibited bilateral diffuse reticular-nodular densities. The diagnosis of lymphocytic interstitial pneumonia was made by fiberoptic bronchoscopy or open lung biopsy. Two patients were treated with corticosteroids, with significant improvement. The third patient died of pneumonia due to Pneumocystis carinii six months after the diagnosis of lymphocytic interstitial pneumonia was established. Serum antibodies to human immunodeficiency virus (HIV) were demonstrable in the two patients in whom the test was performed. Lymphocytic interstitial pneumonia is probably another pulmonary manifestation of AIDS or AIDS-related complex. Although the clinical presentation may be identical to the more common opportunistic infections, the treatment differs, and the prognosis may be better.

Lymphocytic interstitial pneumonia is a rare disease of unknown etiology characterized by interstitial infiltration of the alveolar septae with non-neoplastic mature lymphocytes and plasma cells.1 Lymphocytic interstitial pneumonia has specific clinicopathologic features that distinguish it from other interstitial pneumonias and primary lymphoproliferative disorders of the lung.1-8 Many cases have been associated with dysproteinemias as well as with autoimmune diseases, including amyloidosis, Sjögren's syndrome, myasthenia gravis, chronic active hepatitis, autoimmune hemolytic anemia, chronic thyroiditis, and systemic lupus erythematosus. We report the findings in three patients with lymphocytic interstitial pneumonia in the setting of the acquired immune deficiency syndrome (AIDS) and the AIDS-related complex.

Materials and Methods

The medical records and chest roentgenograms of 150 patients with AIDS or AIDS-related complex who were admitted to the Mount Sinai Hospital in New York between 1981 and 1984 were reviewed. The diagnosis of AIDS was made by criteria established by the Centers for Disease Control.9 The AIDS-related complex was diagnosed when a patient at risk for the development of AIDS (homosexual, intravenous drug abuser, hemophiliac, or Haitian immigrant) had serum antibodies to human immunodeficiency virus (HIV) by enzyme-linked immunoassay (ELISA) or laboratory changes of immune deficiency (reversal of T-helper/T-suppressor cell ratios and reduced mitogenic responses) and developed a clinical syndrome of unexplained fever, weight loss, diarrhea, lymphadenopathy, or oro-esophageal candidiasis, without evidence of malignant disease or prior immunosuppressive therapy. Three (2 percent) of the 150 patients had lymphocytic interstitial pneumonia diagnosed using fiberoptic bronchoscopy or thoracotomy (or both), and their records constitute the basis of this report.

Case Reports

Case 1

A 32-year-old bisexual black man was well until 1978, when he was found to have uveitis. Later that year, he was admitted to a hospital in Los Angeles, complaining of fatigue, weakness, dyspnea, nonproductive cough, diffuse lymphadenopathy, hepatosplenomegaly, and a 13.6-kg (30-lb) weight loss. The pH of arterial blood was 7.46, the arterial oxygen pressure (PaO₂) was 31 mm Hg, and the oxygen pressure (PaO₂) was 59 mm Hg while breathing room air (the calculated alveolar-arterial oxygen difference [P(A-a)O₂] was 51 mm Hg). The chest roentgenogram disclosed bilateral diffuse reticular-nodular densities, and spirometry showed reduced pulmonary volumes. Cultures of sputum for acid-fast bacilli were negative, and the level of angiotensin-converting enzyme was normal. Lymph node biopsy revealed follicular hyperplasia, and liver biopsy showed chronic active hepatitis. The patient underwent fiberoptic bronchoscopy and tranbronchial biopsy, which revealed diffuse interstitial infiltration with mature lymphocytes and plasma cells, without granulomas. He was treated with a course of corticosteroids, with some improvement in symptoms.

In 1981, the patient was admitted to Mount Sinai Hospital in New York because of persistent abnormalities in tests of hepatic function. He underwent another liver biopsy, which demonstrated chronic active hepatitis with transition to cirrhosis, and Epstein-Barr virus was isolated from the sample. At that time, he was noted to have a reversed T-helper/T-suppressor cell ratio (0.2), and immunoelectrophoresis disclosed diffuse hypergammaglobulinemia. Pulmonary function tests continued to show a moderate restrictive impairment, the diffusing capacity was reduced (Table 1), and the chest roentgenogram remained unchanged.

The patient felt well for two years without therapy but was readmitted in 1983 because of recurrent lymphadenopathy, fatigue, weakness, dyspnea, fever, and weight loss, with a worsening of the

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*From the Departments of Medicine and Pathology, Mount Sinai Hospital, New York.
†Instructor in Medicine.
‡Assistant Professor of Medicine.
§Associate Professor of Pathology.
¶Florette and Ernst Rosenfeld and Joseph Solomon Professor of Medicine.

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Reprint requests: Dr. Rosen, Annenberg 24-30, Mount Sinai Hospital, New York, NY 10029

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Table I—Pulmonary Function Test Results in Lymphocytic Interstitial Pneumonia\

<table>
<thead>
<tr>
<th>Data</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>4.05 (78)</td>
<td>1.71 (60)</td>
<td>3.98 (89)</td>
</tr>
<tr>
<td>FEV, L</td>
<td>3.46 (77)</td>
<td>1.24 (58)</td>
<td>3.20 (97)</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>0.85 (110)</td>
<td>0.72 (94)</td>
<td>0.80 (109)</td>
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<tr>
<td>DsL/min/mmHg</td>
<td>10.00 (28)</td>
<td>12.45 (55)</td>
<td>11.64 (44)</td>
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<tr>
<td>Arterial pH</td>
<td>7.42</td>
<td>7.38</td>
<td>7.32</td>
</tr>
<tr>
<td>PaCO, mmHg</td>
<td>34</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>PaO, mmHg</td>
<td>62</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>P(A-a)O, mmHg</td>
<td>45</td>
<td>14</td>
<td></td>
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</tbody>
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*FVC, forced vital capacity; FEV, forced expiratory volume in one second; and PaCO, arterial carbon dioxide tension.

†Numbers within parentheses are percent predicted.

A lymph node biopsy again showed nonspecific hyperplasia. Transbronchial lung biopsy showed interstitial infiltration with mature lymphocytes. The patient then underwent thoracotomy and open lung biopsy, which showed multifocal ill-defined nodules composed of pleomorphic lymphocytes, plasma cells, and monocytes (Fig 2). These changes were characteristic of lymphocytic interstitial pneumonia. Immunopathologic studies performed on frozen tissue demonstrated the presence of a moderate number of plasma cells with intracytoplasmic IgG or IgA, and the lymphocytes contained no detectable intracytoplasmic immunoglobulins. All studies for bacteria, mycobacteria, and fungi were negative. The patient was treated with prednisone (60 mg daily), with rapid improvement in symptoms. With tapering of the dosage of prednisone, he experienced exacerbation of his symptoms, which again improved after increasing the dosage of prednisone.

In January 1984, while the patient felt well, a culture of sputum revealed growth of Mycobacterium avium-intracellulare. No anti-tuberculosis therapy was given, and subsequent cultures of sputum for acid-fast bacilli were negative. Serum antibody to HIV was detected. At present, the patient continues to be chronically ill, but improves receiving prednisone (20 mg on alternate days).

**Case 2**

A 56-year-old black woman with a long history of intravenous drug abuse was admitted, complaining of increasing dyspnea on exertion, cough productive of brownish sputum, fatigue, night sweats, a 9.1-kg (20-lb) weight loss, and chest discomfort. The patient was well until two years before admission, when she presented to another institution in New York City with similar complaints and was found to have an abnormal chest roentgenogram. Evaluation at that time included multiple negative cultures of sputum for acid-fast bacilli, and normal lymph node and bone marrow biopsies. Pulmonary tissue obtained by fiberoptic bronchoscopy and subsequent open lung biopsy reportedly showed lymphocytic interstitial pneumonia. The patient was treated with prednisone, and her symptoms improved. Four months later, she developed a massive hemorrhage from gastric ulcerations, and complete gastrectomy and esophagojejunosotomy were performed. Therapy with prednisone was tapered and discontinued.

On admission the patient was a thin black woman in moderate respiratory distress. Bibasilar crackles were audible in the chest. Serum protein and immune protein electrophoresis revealed a polyclonal elevation of IgG. Analysis of arterial blood gas levels repeatedly showed a PaO2 between 71 and 80 mm Hg while breathing room air. Chest roentgenograms revealed bilateral diffuse interstitial and alveolar densities (Fig 1B). Computerized tomography of the chest and abdomen confirmed the presence of scattered infiltrates throughout both pulmonary fields, as well as slight splenomegaly. Pulmonary function tests revealed a restrictive impairment, and the single-breath carbon monoxide diffusing capacity (Dab) was reduced (Table I). A lung scan with 99mTc albumin showed several large focal areas of increased activity in the right middle and left lower lobes. The patient had a 7-mm area of induration in response to 5 tuberculin units of purified protein derivative of tuberculin (PPD), but was unresponsive to controls. The Thelper/T-suppressor cell ratio was reduced to 0.6. Multiple smears of sputum were negative for acid-fast bacilli. The patient underwent fiberoptic bronchoscopy, washings and brushings were negative for bacterial growth and acid-fast bacilli. Histologic examination of the transbronchial biopsy showed nonspecific peribronchial chronic inflammation and mild interstitial fibrosis. The patient underwent a lymph node biopsy, which on microscopic section showed diffuse hyperplasia with a mixed population of T-cells and polyclonal B-cells. She subsequently underwent left thoracotomy and open lung biopsy, which established the diagnosis of lymphocytic interstitial pneumonia. Immunohistologic staining of the pulmonary tissue revealed that the lymphocytes were T-cells, with approximately equal numbers of helper and suppressor cells.

The patient was given prednisone (40 mg daily), with improvement in her respiratory symptoms, but she continued to be febrile. She then underwent bone marrow biopsy, which showed granulocytic hyperplasia with a mild increase in plasma cells and monoclonal cells and a focal increase in reticulin; special stains disclosed numerous acid-fast bacilli. A liver biopsy showed chronic persistent hepatitis without granulomas or acid-fast bacilli. The patient was empirically given isoniazid (300 mg), ethambutol (1,200 mg), rifam-

![Figure 1. Chest roentgenograms in patients with lymphocytic interstitial pneumonia associated with AIDS or AIDS-related complex. A (left), B (center), and C (right) correspond to patients 1, 2, and 3, respectively. All patients had bilateral pulmonary infiltrates. Patient 2 demonstrated blunting of right costophrenic angle as consequence of prior open lung biopsy.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21554/ on 06/26/2017)
months later, he died at another institution as a result of fulminant pneumonia due to Pneumocystis carinii.

DISCUSSION

In 1981, an outbreak of unusual malignant diseases and opportunistic infections in male homosexuals and intravenous drug abusers of both sexes was recognized, which eventually became known as AIDS.46-48 Later, Haitian immigrants, patients with hemophilia A, and individuals who received transfusions of blood products were also recognized as being at risk for the development of the disease.49-51 AIDS-related complex was later described in individuals from the major risk groups and was believed to represent a related disorder that may progress to full-blown AIDS.49,52

Human immunodeficiency virus (HIV) is believed to be the cause of both AIDS-related complex and AIDS.49-70 This retrovirus is very closely related to HTLV-I and HTLV-II, which are strongly implicated in malignant T-cell proliferation.53

An increased incidence of B-lymphocyte proliferative disorders and malignant diseases has also been described in patients with AIDS.51-73 Most patients have either nonspecific reactive lymph node hyperplasia or diffuse large cell or immunoblastic lymphomas of the brain, bone marrow, or lymph nodes. Lymphocytic interstitial pneumonia, a disorder characterized by pulmonary infiltration with mature lymphocytes and plasma cells, has been found recently in the children of mothers in groups at high risk for AIDS,76 and the Centers for Disease Control have expanded the case definition of the syndrome for national reporting to include chronic lymphocytic interstitial pneumonia in children under 13 years of age, unless tests for HIV are negative;41 however, adults with lymphocytic interstitial pneumonia are not yet considered to meet this definition, in spite of four recent reports that have noted the presence of lymphocytic interstitial pneumonia in adult patients belonging to groups at high risk for developing AIDS. Saldana and associates80 first described six Haitian immigrants with lymphocytic interstitial pneumonia, two of whom subsequently developed AIDS. Grieco and Chinoy-Acharya81 later described a homosexual man with lymphocytic interstitial pneumonia, oral and esophageal candidiasis, and abnormalities of immunologic function characteristic of AIDS, but results of studies for HIV antibody were not reported. Solal-Celigny and associates82 reported the findings in one patient from Haiti and two from Central Africa with lymphocytic interstitial pneumonia, lymph node hyperplasia, and lymphoid infiltrates in other visceral organs; HIV antibodies were detected in the two patients in whom these studies were performed.82 Finally, Ziza and associates83 described a Haitian woman with lymphocytic interstitial pneumonia and immunologic abnormalities typical of AIDS. Moreover, the serum titer of

CASE 3

A 46-year-old homosexual black man with a history of chronic fever, weakness, malaise, chronic diarrhea, diffuse lymphadenopathy, and oral candidiasis was admitted to Mount Sinai Hospital in New York, because of increasing dyspnea, weight loss, and nonproductive cough. The chest roentgenogram showed a diffuse increase in interstitial markings. The patient underwent fiberoptic bronchoscopy, which revealed interstitial fibrosis, and no organisms were demonstrated. He was discharged from the hospital with no therapy.

The patient was readmitted five months later because of worsening fever, cough, and dyspnea. The chest roentgenogram showed worsening of the reticulonodular densities (Fig 1C). Examination of the chest revealed bilateral lower lobe inspiratory crackles. Protein electrophoresis revealed diffuse hypergammaglobulinemia. Three smears of sputum were negative for acid-fast bacilli. Pulmonary function tests showed a reduced DLco (Table 1). The T-helper/T-suppressor cell ratio was reduced at 0.26, and reduced mitogenic responses were found in vitro. The patient underwent fiberoptic bronchoscopy, which revealed a multifocal interstitial lymphohistiocytic infiltrate consistent with lymphocytic interstitial pneumonia. The patient was again discharged with no therapy. Six
Lymphocytic Interstitial Pneumonia and AIDS (Moms et al)

Lymphocytic antibody to HIV was 1:640, and the virus was isolated from both blood and fluid obtained by bronchoalveolar lavage. These investigators speculated that pulmonary infection with HIV may play a role in the development of lymphocytic interstitial pneumonia.

The diagnosis of lymphocytic interstitial pneumonia is usually made by open lung biopsy; however, in instances such as patient 3, where a large fragment of pulmonary tissue was obtained by transbronchial lung biopsy, the diagnosis can be established. The three patients with lymphocytic interstitial pneumonia presented herein belonged to groups at high risk for the development of AIDS. Further evidence for the presence of AIDS in these individuals includes the finding of M avium-intracellulare infection in one, death from pneumonia due to P carinii in another, and the presence of antibodies to HIV in the two individuals who were tested, and abnormal T-helper/T-suppressor ratios in all three. Their presenting complaints of dyspnea, nonproductive cough, weight loss, and fever were similar to previously reported cases of lymphocytic interstitial pneumonia but are also typical of symptoms seen in patients with pneumonia due to P carinii and other opportunistic pulmonary infections seen in patients with AIDS. The findings on the chest roentgenogram, restrictive impairment seen on spirometry, and reduction in Dsb are also compatible with both lymphocytic interstitial pneumonia and opportunistic pulmonary infections. Pulmonary isotopic uptake during 67gallium scanning is also characteristic of infection with P carinii, although there are no previous reports of 67gallium scanning in patients with lymphocytic interstitial pneumonia. Therefore, in each of these patients, the most likely diagnosis was pneumonia due to P carinii or another opportunistic pulmonary infection, and lymphocytic interstitial pneumonia was not suspected.

Two patients were treated with corticosteroids, with a significant improvement in symptoms, chest roentgenograms, and pulmonary function. Patient 1 has required several courses of corticosteroids because of relapsing disease. This experience contrasts with that in the literature, where poor or irregular responses to corticosteroid therapy occur. At the present time, two patients are alive but chronically ill. Previous cases of lymphocytic interstitial pneumonia have had variable outcomes, with approximately one-third to one-half of the patients dying within five years. Our patients are alive at seven years and 3½ years after the onset of the disease. In each case the patients' symptoms and objective findings improved with corticosteroid therapy.

The etiology of lymphocytic interstitial pneumonia is unknown. An abnormality of the immune system is likely, since lymphocytic interstitial pneumonia is commonly associated with other immune disorders, including Sjögren's syndrome, myasthenia gravis, chronic active hepatitis, and systemic lupus erythematosus. Furthermore, the frequent occurrence of either hypogammaglobulinemia or hypergammaglobulinemia suggests that disordered immune regulation plays a role in the pathogenesis of lymphocytic interstitial pneumonia. Immunochemical staining has demonstrated that the infiltrating lymphocytes in lymphocytic interstitial pneumonia are polyclonal B-lymphocytes. It is intriguing that patients with AIDS frequently demonstrate polyclonal B-lymphocyte activation and hypergammaglobulinemia and often develop autoimmune phenomena such as thrombocytopenia and the presence of antinuclear antibodies. In the setting of B-cell proliferation, patients with lymphocytic interstitial pneumonia and others with AIDS have developed malignant B-cell lymphomas.

As opposed to the proliferation of B-lymphocytes seen in the lungs of previously reported cases of lymphocytic interstitial pneumonia, both of our patients in whom immunochemical staining was performed showed predominance of T-lymphocytes. In patient 1, these cells were almost exclusively T-suppressor cells, and patient 2 showed almost equal proportions of T-helper and T-suppressor cells. Fluid from bronchoalveolar lavage in patients with AIDS and various pulmonary infections, as well as in one patient with lymphocytic interstitial pneumonia, typically shows a predominance of T-suppressor cells. It is possible that this accumulation of lymphocytes in the lung, perhaps in response to HIV or another pathogen, is crucial to the development of lymphocytic interstitial pneumonia in patients with AIDS.

Between 1981 and 1984, there were six patients diagnosed as having lymphocytic interstitial pneumonia at Mount Sinai Hospital, New York. Three of these patients had AIDS or the AIDS-related complex. This frequency is much higher than is expected by chance alone. The clinical presentation of lymphocytic interstitial pneumonia is quite similar to that of many opportunistic pulmonary infections, particularly pneumonia due to P carinii. In this series, two of three patients were treated with systemic corticosteroids, with significant improvement in symptoms and objective measurements, and one has survived for seven years.

Although no causal relationship between HIV infection and lymphocytic interstitial pneumonia has been established, the simultaneous occurrence of these disorders in our series and others suggests that lymphocytic interstitial pneumonia is part of the spectrum of HIV-related disease.

The clinical presentation of lymphocytic interstitial pneumonia may be identical to an opportunistic pneumonia. Establishing the correct diagnosis by lung biopsy is essential, since treatment of lymphocytic...
interstitial pneumonia with corticosteroids may be effective, and the prognosis appears to be better than with the more common opportunistic infections.

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