Lymphoid Interstitial Pneumonia*

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Three cases of lymphoid interstitial pneumonia (LIP) are described. Lung biopsies demonstrated a similar characteristic histologic appearance of diffuse interstitial lymphocytes. Two had increased IgM. One patient developed a reticulum cell sarcoma. All were treated with prednisone but only one improved.

Lymphoid interstitial pneumonia (LIP) is one of a series of parenchymal pulmonary diseases discovered in the last few years. LIP has the histologic features of benign pseudolymphoma but it is more diffuse.1 In LIP there is a predominance of mature lymphocytes in the interstitium of the lung which at times forms germinal centers. The process surrounds, but does not invade, structures normally present. A true lymphoma infiltrates the lung homogeneously, by surrounding and invading structures including larger bronchi and lymph nodes.2 The absence of involvement of local lymph nodes and of extrapulmonary tissues differentiates LIP from malignant lymphoma.14

Fourteen cases of histologically characteristic LIP have been reported.1,3-5 The etiology remains unknown. The clinical features of this disorder have not been clearly defined. Pulmonary function has not been previously described. This report presents the varying clinical, physiologic and immunologic features of LIP as demonstrated by three patients.

Case Reports

Case 1

A 47-year-old plywood worker, nonsmoker, was admitted to the Veterans Administration Hospital, Durham, NC, on June 26, 1968 because of progressive dyspnea. He was wounded in the chest during World War II and had schrapnel removed. Since that time he has complained of mild dyspnea on exertion of climbing two flights of stairs. He also developed a chronic cough of 15 years' duration productive of about 15 ml of whitish sputum per day. In 1961 he experienced hemoptysis consisting of streaks and small flecks of blood. Bronchoscopy and bronchography showed no abnormalities of the bronchial tree. Six months preceding this admission exertional dyspnea became so pronounced he could climb only six to eight steps. Repeated episodes of sharp, right parasternal pains in association with coughing and deep breathing occurred. A weight loss of 40 pounds was documented.

On admission his respiratory rate was 36. On deep breathing the chest expanded fully and there was intercostal and supraclavicular retraction. No rales were heard. There were no cardiac abnormalities. The liver and spleen were not palpable. Lymph nodes were not enlarged. There was no parotid or sublingual gland enlargement. Laboratory examination revealed a white blood cell count of 8,200 with a normal differential. Sputum culture showed no growth. The result of cytologic examination was negative and the elec

Figure 1. Chest roentgenograms of case 1 demonstrating a diffuse infiltrate with a mixed interstitial and alveolar process.
trocardiogram showed right axis deviation and right bundle branch block. Both the intermediate tuberculin and the histoplasmin skin tests were positive, measuring 7 mm at 48 hours. Chest films showed a diffuse, patchy infiltrate throughout both lung fields which was considered to be a mixed interstitial and alveolar process (Fig 1.). The bone marrow aspirate was normal in cellularity and differentiation of blood cell precursors. Both the vital and total lung capacities were markedly decreased while flow rates were normal (Table 1) indicating a severe restrictive respiratory defect. A steady-state carbon monoxide diffusing capacity was normal. Arterial blood gas analysis indicated mild hypoxemia and hyperventilation. On July 6, 1988, an open lung biopsy of the right lower lobe was performed. The alveolar and peribronchial interstitial tissue was markedly thickened by heavy cellular infiltrate composed largely of lymphocytes and a few plasma cells (Fig 2). Multiple, small focal collections of giant cells containing cholesterol clefts and scattered small focal calcifications were also present. Immunoglobulin deposition in the lung could not be demonstrated by immunofluorescent technique using anti IgA, IgM and IgG. In August, 1988, the right lung was irradiated with 540 rads. One month later there was no improvement in the chest film, total lung volume, vital capacity or arterial oxygen tension. With exercise arterial hypoxemia became pronounced (Table 1). IgM was elevated and the antinuclear factor was positive (Table 1).

**Figure 2a** (right, upper). Open lung biopsy in case 1. This field reveals the diffuse interstitial inflammatory infiltration without recognizable fibrosis (× 40). **2b** (right, lower). A higher magnification of the biopsy in case 1 to show that virtually all of the infiltrating cells are lymphocytes. Alveolar surfaces are lined by cuboidal epithelium. The intra-alveolar macrophages are not increased (× 100).

**Table 1—Pulmonary Function Tests.**

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Date</td>
<td>8/15/68</td>
<td>5/01/70</td>
<td>1/06/70</td>
</tr>
<tr>
<td>VC [L (% pred)]</td>
<td>1.78 (40.4%)</td>
<td>2.22 (50%)</td>
<td>2.72 (60%)</td>
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<tr>
<td>FEV₁ [L]</td>
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<td>2.00 (90%)</td>
<td>2.40 (88.4%)</td>
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<tr>
<td>MMEF [L]</td>
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<td>2.66 (77%)</td>
<td>3.53 (81%)</td>
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<td>RV [L]</td>
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<td>1.25</td>
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<tr>
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<td>3.19 (50%)</td>
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<td>MVV [L]</td>
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<td>72.2</td>
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<tr>
<td>Dlco (cc/min/mm Hg)</td>
<td>16.2*</td>
<td>27.71</td>
<td>19.08†</td>
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<td><strong>Room Air</strong></td>
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<td></td>
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</tr>
<tr>
<td>PaO₂ [mm Hg]</td>
<td>79</td>
<td>73</td>
<td>90</td>
</tr>
<tr>
<td>PacO₂ [mm Hg]</td>
<td>44</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>pH</td>
<td>7.44</td>
<td>7.42</td>
<td>7.43</td>
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<tr>
<td>O₂Sat%</td>
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<td>95</td>
<td>97</td>
</tr>
<tr>
<td>VD/VT</td>
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<td>.3</td>
<td>.3</td>
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<tr>
<td>D(A-a)O₂ [mm Hg]</td>
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<td><strong>100% O₂</strong></td>
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<td>PaO₂ [mm Hg]</td>
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* = Steady state. † = Single breath.
2). In September, 1968, prednisone in the amount of 40 mg per day was begun. The dose was reduced to 20 mg per day after one month. This dose was maintained until October, 1969, when the medication was gradually discontinued. On this treatment there was some improvement in the patient's dyspnea. However, pulmonary function studies did not improve (Table 1). Dyspnea has not changed after therapy was terminated. When the patient was last seen in May, 1972, his symptoms, physical examination, pulmonary function and chest film remained unchanged.

CASE 2

A 27-year-old white man sought admission to Duke Hospital for a persistent cough of 16 months' duration. Dyspnea on exertion was first noted six months previously. Over the preceding three months his exercise tolerance progressively decreased. For the ten days preceding admission he was frequently awakened at night with paroxysms of coughing. There was no wheezing, hemoptysis, fever, chest pain or weight loss. For the preceding four years, the patient had worked in a machine room making nylon fiber. Although the atmosphere was not dusty, his symptoms were worse while at work. Sudden change in temperature also initiated paroxysms of coughing. Skin tests with intermediate PPD, blastomycin, histoplasmin and coccidioidin gave negative results. An extract of dust taken from the factory in which he worked was used for skin testing and there was no reaction either immediately or during the next 48 hours.

The patient was obese. His blood pressure was 110/70, pulse rate was 65 and regular and the respiratory rate was 34 per minute and shallow. The skin, especially over the chest, was mildly erythematous throughout and there was dermatographia. Lymph nodes were not enlarged. Good respiratory excursions were present without intercostal retraction. Fine cracking rales were heard at both bases. The liver, spleen and salivary glands were enlarged. Chest film revealed no infiltrates (Fig 3). The vital capacity was decreased with an increase in residual volume and mildly decreased flow rates indicating mild obstructive disease (Table 1). Severe arterial hypoxemia and mild hypercapnia were present. Resting alveolar-arterial oxygen difference was increased while breathing room air and 100 percent oxygen. The single-breath carbon monoxide diffusing capacity was normal.

An open thoracotomy was performed and a biopsy of the lingula was obtained in May, 1967. Cultures of the lung tissue showed no growth of bacteria. The microscopic examination showed an interstitial infiltration of plasma cells and lymphocytes surrounding bronchioles in a diffuse as well as nodular pattern (Fig 4). A rare focus of multinucleated giant cells was seen. An occasional macrophage with foamy cytoplasm was noted in the alveoli. The patient was started on prednisone, 60 mg per day for ten days. The dose was then reduced to 20 mg per day and the patient discharged.

He was readmitted in September, 1967, for reevaluation. During the previous three months he had been taking 5 mg of prednisone per day. On admission the temperature was 37°C; blood pressure was 130/80; the pulse was 70 per minute and the respiratory rate was 16 per minute. Rales were no longer present at the lung bases.

A second pulmonary biopsy was performed in September, 1967. The microscopic examination showed small numbers of macrophages with foamy cytoplasm within thickened fibrous septa. There were focal interstitial collections of lymphocytes and small granulomas with central epithelioid cells. No acid-fast bacilli or fungi were seen in the specimen in the specially stained sections.

In April, 1968, an increase in the total lung capacity and vital capacity was noted. His prednisone was discontinued.
Serum immunoglobulin studies showed a low normal IgG, normal IgA and a high normal IgM in October of 1968 (Table 2). When he was last seen in June, 1971, he continued to be asymptomatic with normal pulmonary function tests and chest film.

CASE 3

A 54-year-old chemical engineer was well until November, 1964, when he noted the onset of a nonproductive cough. There was no chest pain, dyspnea, fever or hemoptysis, but over the next four months he lost seven pounds in weight. A chest film had been normal in 1962. The chest film taken in November, 1964, showed diffuse interstitial infiltrate predominating in the upper lobes. An open thoracotomy was performed and a biopsy of the lingula was reported as showing "lymphocytic pneumonia." He was discharged on no therapy, but his cough persisted. From January to March, 1966, he received 20 mg of prednisone per day, but his dry cough continued and the chest film remained unchanged. The drug was then discontinued. From 1962 to 1968 there had been a gradual weight loss of 45 lbs. A nonproductive cough persisted.

On admission to the Duke University Medical Center in October, 1968, his blood pressure was 120/80, the pulse rate was 72 and the respiratory rate was 22. There were fine crackling and end-expiratory rales at both apices posteriorly and in the supraclavicular spaces bilaterally. Coarse rales were heard in the right mid lateral lung area. There were no cardiac abnormalities. The liver was palpable 7 cm below the right costal margin. There was no generalized adenopathy and the salivary glands were not enlarged.

Bone marrow aspirate was normal. A chest film showed a diffuse irregular, interstitial, patchy, nodular infiltrate predominantly in both upper lobes similar to that observed four years earlier (Fig 5). There were a few areas of linear densities in the lower lobe. The skull films and an excretory urogram were normal. Results of intermediate PPD, histoplasmin, blastomycin and coccidioidin skin tests were negative. Intradermal skin test with Candida albicans was 4 mm and mumps was 7 mm at 48 hours. A radioactive scan demonstrated a space occupying lesion in the right lobe of the liver and in the spleen. A splenectomy and biopsies of the liver were performed. The spleen weighed 450 grams. Microscopic sections of the spleen and liver showed a highly
anaplastic pleomorphic reticulum cell sarcoma. The cell types of the previous lung biopsy (Fig 6a) were different from the cell types in the liver and spleen (Fig 6b). The patient was started on cyclophosphamide on (Cytoxan) and vincristine and discharged from the hospital. Pulmonary function tests were normal (Table 1). Serum immunoglobulin showed a low normal IgG, normal IgA and increased IgM. Test results for rheumatoid factor and antinuclear factor were negative. In the subsequent 18 months his respiratory symptoms of dry cough and mild dyspnea on exertion are unchanged. A therapeutic program of cyclophosphamide 100 mg per day and vincristine 1 mg intravenously every two weeks has been continued to the present. Liver size has decreased but the hepatic scan is unchanged.

**DISCUSSION**

Thirteen patients with LIP, including three children, were reported by Carrington and Liebow. Three of their initial cases improved with adrenal cortical steroids. A subsequent report by those authors stated that the expected improvement with steroid therapy did not occur. A patient with myasthenia gravis, LIP and an IgG monoclonal gammapathy has been described by Montes and associates. A lung biopsy was performed on another patient who had Sjögren's syndrome associated with a vasculitis and macroglobulinemia. He had fever, shaking chills, cyanosis and hemoptysis. Chest film demonstrated a diffuse interstitial infiltrate. The histologic sections were reviewed and LIP was confirmed. At autopsy, two years later, interstitial pulmonary fibrosis was found. The patients currently described had diffuse interstitial lymphocytic involvement of both lungs. Symptoms in previously described patients have included cough, dyspnea, fever and weight loss. Chronic cough was present in the three patients currently described, but exertional dyspnea was more prominent only in two. Fever was not observed.

Radiologic studies of the chest show the initial appearance of bilateral patchy nodular densities prominent at the lung bases. Peripheral linear densities resembling Kerley B lines are also observed. As the disease progresses densities tend to become confluent. Patients 1 and 3 of this report had chest films resembling the previously described cases. Patient 2 had no infiltrate.

Pulmonary function in LIP has not been previously described. Patient 1 had a restrictive ventilatory pattern which has persisted. Patient 2 had a mild obstructive ventilatory pattern and hypoxemia which markedly improved with steroid therapy. In patient 3, normal pulmonary functions and blood gases have been observed, two years after a diagnostic biopsy. Therefore, observable pulmonary involvement may be present in the absence of a physiologic defect demonstrable by tests used.

Bronchiolar compression or narrowing because of an infiltrative process could account for an obstructive pattern. Histologic evidence for bronchiolar compression has been demonstrated. It could improve as the infiltrate subsides. Additionally, the infiltrative process could reduce lung volume and possibly decrease compliance by replacing normal lung tissue and producing fibrosis.

A monoclonal gammapathy (IgG) was previously described in one patient with LIP and myasthenia gravis. Patient 1 had elevated IgM associated with a homogeneous positive antinuclear factor. During his course of prednisone, immunoglobulin levels decreased and antinuclear factor was intermittently positive. Normal immunoglobulin concentrations were obtained from patient 2 but after his course of therapy and clinical improvement. It appears that both patients 1 and 3 had an acquired dysgammaglobulinemia.

The response to steroid therapy was minimal in two patients but distinct gradual improvement in case 2 has continued to the present. This type of therapy was previously reported to be of little benefit.

The clinical course of the patients being described is also divergent. One patient has become asymptomatic while another has developed a reticulum cell sarcoma of the liver and spleen. The third case has remained unchanged for two years. Long-term evaluations on previously described cases are not reported.

The origin of the difference between localized pseudolymphoma and diffuse LIP could be different responses to similar stimuli or the same response, varying in magnitude, to similar or different inciting agents. Another possibility is that LIP may be only one type of reaction by the lung in response to various environmental stimuli. The cellular infiltrate might be only an intermediate step with resultant healing in the form of interstitial fibrosis.

The lung parenchyma when in contact with airborne haptens or antigens has three major modes of reaction. Immediate hypersensitivity can occur in the form of acute bronchospasm as in response to pollens. An example of the Arthus type of reaction with circulating precipitins is farmer's lung. Delayed hypersensitivity reaction is the classic tuberculin type of hypersensitivity. LIP with its cellular response may indicate a form of delayed hypersensitivity to a chronically inhaled antigen and may be the result of various antigenic stimuli.

Autoimmune diseases, such as Hashimoto's disease and Mikulicz syndrome, have a similar lymphocytic infiltrate. The antigenic environmental stimulus might in some way alter the lung parenchyma to form a new complex antigen.
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(hapten and altered lung tissue). Therefore, autoantibodies may be formed to this newly altered lung tissue, which may even have the ability to cross react with other organ systems forming an autoimmune illness.9

The etiology of LIP at the present time remains obscure.

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Modern Pathfinder in Child Psychology

Jean Piaget, the Swiss psychologist, has elaborated a general theory of intellectual development which, in its scope and comprehensiveness, rivals Freud's theory of personality development. Piaget proposes that intelligence—adaptive thinking and action—develops in sequence of stages that is related to age. Each stage sees the elaboration of new mental abilities which set the limits and determine the character of what can be learned during that period. The ages at which the stages evolve will depend upon the native endowment of the child and upon the quality of the physical and social environment in which he is reared. "The principle goal of education," he once said, "is to create men who are capable of doing new things, not simply repeating what other generations had done—men who are creative, in-
ventive and discoverers. The second goal of education is to form minds which can be critical, can verify, and not accept everything they are offered." The International Center for Genetic Epistemology, which Piaget founded in 1935 with a grant from the Rockefeller Foundation, continues to draw scholars from around the world who wish to explore with Piaget the origin of scientific concepts. As Professor of Experimental Psychology at the University of Geneva, Piaget also continues to teach courses and conduct seminars.

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