Human Immunodeficiency Virus-related Lymphocytic Alveolitis

Jean-Marcel Guillon, M.D.;* Brigitte Autran, M.D.;† Michel Denis, M.D.;* Pierre Fouret, M.D.;‡, Fernando Plata, Ph.D.1,§ Charles M. Mayaud, M.D.;* and Georges M. Akoun, M.D., F.C.C.P.*

We observed 276 HIV-infected patients to determine the frequency, degree, and clinical presentation of the lymphocytic alveolitis in different stages of HIV disease, and also to identify the lymphocyte subsets involved. In 154 patients with proved lung infections or tumors (group A), bronchoalveolar lavage fluid showed lymphocytosis in 78 percent of cases. In 122 subjects (31 AIDS and 91 non-AIDS patients) without evidence of lung tumor or infection (group B), lymphocytic alveolitis was seen in 72 percent of cases. In 61 of 88 (69 percent) group B lymphocytic patients, we observed respiratory symptoms or diffuse interstitial opacities; however, we also observed such alveolitis in 27 of 46 (59 percent) group B patients free of respiratory symptoms and abnormality of chest x-ray film. This alveolitis was seen not only in AIDS or ARC patients but also at earlier stages of HIV infection. T-lymphocyte analysis showed a large majority (40 to 93 percent) of CD8 positive lymphocytes in the 37 patients tested. A dual fluorescence analysis revealed, in 18 subjects, that those cells were phenotypically cytotoxic (CD8 + D44 +). These findings suggest that, regardless of HIV-infection stages and of opportunistic lung infections, a CD8-positive T-lymphocyte alveolitis may be present in HIV-infected patients and could be responsible for cough, dyspnea, interstitial pneumonitis, and abnormalities of pulmonary function tests. (Chest 1988; 94:1264-70)

During the course of the acquired immunodeficiency syndrome (AIDS), the lung appears to be a special target organ for both opportunistic and common bacterial infections; a nonspecific interstitial pneumonitis is also common. Previous studies using bronchoalveolar lavage (BAL) in AIDS patients with pneumonitis and in AIDS-related complex (ARC) patients frequently showed a lymphocytic alveolitis. Little is known about the frequency, the importance, and the cause of this alveolitis in the different stages of human immunodeficiency virus (HIV) disease.

We undertook this investigation to identify the pulmonary cell populations in 276 HIV-positive subjects divided into two groups based on the presence (group A) or absence (group B) of proved lung infectious or tumor processes. This study is the first to our knowledge to correlate the clinical, radiologic, and pulmonary function test findings with the lymphocytic alveolitis we showed in the two groups of patients. A lymphocytic alveolitis was present not only in AIDS and ARC patients but also in 54 percent of seropositive healthy carriers (SPC) and in 59 percent of patients with a prolonged generalized lymphadenopathy (PGL). Furthermore, in the eight group A and the 29 group B patients tested, we demonstrated that this alveolitis was composed of CD8 + lymphocytes, and, in 18 patients of different subgroups, a dual fluorescence analysis revealed a considerable increase of alveolar CD8 + D44 + cytotoxic T-lymphocytes (CTLs). The significance and pathogenesis of this alveolitis are discussed.

Material and Methods

Patient Population

BAL was performed on 276 HIV-infected patients from January 1984 to March 1987. An informed consent for the lavage procedure was obtained from all patients. We evaluated 256 men and 20 women aged 18 to 79 years; 259 patients belonged to well-defined risk groups: 212 homosexual men, 21 IV drug abusers, two hemophiliacs, eight transfusion recipients, ten Haitians, five African residents, and one sexual partner of a known HIV-infected subject.

Two groups of patients were distinguished. Group A was composed of 154 patients with a proved pulmonary infection or tumor. Common bacterial infections (CBI) were diagnosed in 18 cases; these patients had bronchitis or lobar or segmental pneumonia, and various pathogens were found: Streptococcus pneumoniae, Hemophilus influenzae, B catarhali, Escherichia coli, and Staphylococcus aureus. This subgroup was composed of two seropositive carriers, two ARC and 14 AIDS patients. Seven patients had pulmonary tuberculosis. Opportunistic infections (OI) were diagnosed in 116 cases: pneumonia due to Pneumocystis carinii in 108 cases, cytomegalovirus in four cases (of which two were associated with P carinii), cryptococcosis in two cases, herpes and toxoplasmosis in one case each, and nontuberculous mycobacteria in two cases (M xenopi). Finally, there were also 13 pulmonary localizations of a Kaposi's sarcoma (KS).

Group B consisted of 122 patients without evidence of pulmonary infection or tumor despite the same diagnostic procedures than in group A. There were 24 seropositive healthy carriers (SPC), 17 had a prolonged generalized lymphadenopathy (PGL), 50 were ARC, and 31 were AIDS, of whom eight had an extrathoracic OI (cerebral toxoplasmosis, cryptosporidiosis), and 23 had an extrapulmonary

* Chest Disease Department, Hôpital Tenon, Paris, France.
† Laboratory of Cellular Immunology, Hôpital Pitié-Salpêtrière, Paris.
‡ Laboratory of Pathology, Hôpital Tenon, Paris.
§ Laboratory of Biology and Immunology of Retrovirus, Institut Pasteur, Paris.

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KS. Seventy-six patients presented with respiratory symptoms or abnormal chest x-ray film, and 46 patients were completely asymptomatic.

No statistical difference could be detected between groups A and B regarding the mean age (37 ± 3), the male/female ratio, or the smoking status.

**Diagnostic Procedures**

The HIV seropositivity was assessed using both an ELISA and a Western-blot analysis. The HIV infection stage was established according to the Centers for Disease Control’s criteria. All patients underwent the same diagnostic procedures for pulmonary disease.

Diagnosis of common bacterial infection was made using transtracheal aspiration or protected brush catheter before the BAL. Pulmonary KS was diagnosed on characteristic endoscopic appearance (six cases) or bronchial biopsy specimen (five patients) or open lung biopsy (five cases).11

In all subjects BAL was done as previously described10 and performed by wedging the bronchoscope in a subsegment of the lung (usually the middle lobe or the lingula). A maximum of 300 ml of 0.9% saline solution was instilled in 50-ml aliquots and aspirated back by manual suction. If an inadequate return of fluid was obtained (less than 70 ml), the patient was excluded from the study. Samples of pooled lavage, including the initial aliquot, were dispatched to different laboratories for clinical diagnostic studies and T-lymphocyte analysis. The total number of cells present was determined by hemocytometer; differential cell counts were performed on Giemsa’s stained cytospin preparation. Results were expressed as the percentage of total cells. Absolute numbers were estimated by multiplying the percentage of each cell subset by the mean cell concentration in lavage fluid. Normal values are those described in literature,10,11 i.e., cellularity, 120 ± 50 x 10^6 cells/ml, of which 91 ± 4 percent are macrophages, 1 ± 1 percent are polymorphonuclear cells (PMC), and 8 ± 2 percent are lymphocytes with 50 ± 10 percent CD4 + , 30 ± 7 CD8 + T cells (r = 1.8 ± 0.7), and 10 ± 5 percent B cells.

In all patients we routinely performed the same microbiologic studies including direct examination of touch imprints (Giemsa, Gram-Weigert, Ziel-H-Nielsen, and modified Grocott stains); culture for bacteria, mycobacteria, fungi and viruses; immunofluorescence assay for virus (cytomegalovirus, herpes, adenovirus) and for Legionella and Cryptococcus antigens. During cytologic examination, we also looked for intracytoplasmic or intranuclear viral inclusion bodies, malignant cells, hemosiderin-laden macrophages, and atypical bronchial or alveolar lining cells.

Transbronchial lung biopsy was never performed in our institution. Open lung biopsy (OLB) was carried out on ten patients with severe progressive pulmonary disease in whom results of the diagnostic procedures were negative.

**T-Lymphocyte Analysis**

Alveolar lymphocytes were separated from alveolar macrophages by a two-hour adherence on plastic. Lymphocyte subsets were analyzed with a single labeling procedure using the following monoclonal antibodies (moAbs): IOT3 (CD3) and IOT4 (CD4) (Immunotech), and T8-RD (CD8, Coultronics). The double labeling procedure was performed using the D44 moAb, which reacts with CD4 + lymphocytes and CD5 + cytotoxic cells but not with CD8 + suppressor cells.13 Briefly, cells were incubated with moAbs then, with a fluorescein-isothiocyanate (FITC) coupled goat anti-mouse IgG F(ab')2 serum (Cappel Lab). For CD8-D44 double staining, FITC-labeled washed cells were incubated with the phycoerythrin conjugate T8 moAb. Positive control samples were single stained with the D44 or the T8 moAbs alone. Each incubation was performed at 4°C for 20 minutes. Cells were analyzed for their fluorescence in an argon ion laser cytometer (FACSTAR, Becton Dickinson).

**Pulmonary Function Studies**

Pulmonary function tests included spirometric study, lung volumes, flow rates, single-breath carbon monoxide diffusing capacity, and exercise testing measuring arterial blood gas values.

**Statistical Analysis**

All data are expressed as mean ± SE. Statistical analyses were done with unpaired Student’s t test or Wilcoxon signed rank test.

**RESULTS**

We evaluated 276 HIV-infected patients divided into two groups. In group A, 154 patients had a proved pulmonary infection or tumor, and in group B, 122 patients had no evidence of a lung infectious or tumor process despite the same diagnostic procedures as in group A.

**Cellular Characteristics of Lavage Fluid**

Alveolar lymphocytosis was defined as more than

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**Table 1—Frequency and Degree of Alveolar Lymphocytosis Among Subgroups of Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No.</th>
<th>Patients With Lymphocytosis, %</th>
<th>BAL Fluid Returned, ml</th>
<th>Mean cell Concentration, x10^6/ml</th>
<th>Macrophages†</th>
<th>PMC†</th>
<th>Lymphocytes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBI</td>
<td>18</td>
<td>8 (45)</td>
<td>90 ± 15</td>
<td>320 ± 95</td>
<td>61 ± 7</td>
<td>16 ± 8</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7</td>
<td>5 (72)</td>
<td>132 ± 10</td>
<td>298 ± 75</td>
<td>64 ± 9</td>
<td>9 ± 6</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>KS</td>
<td>13</td>
<td>10 (77)</td>
<td>93 ± 8</td>
<td>260 ± 52</td>
<td>64 ± 5</td>
<td>1.5 ± 0.5</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>OI</td>
<td>116</td>
<td>98 (85)</td>
<td>102 ± 3</td>
<td>254 ± 34</td>
<td>51 ± 2</td>
<td>11 ± 1</td>
<td>38 ± 2</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulm OI</td>
<td>8</td>
<td>5 (63)</td>
<td>107 ± 20</td>
<td>170 ± 32</td>
<td>65 ± 8</td>
<td>8 ± 6</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>extrapulm KS</td>
<td>23</td>
<td>20 (87)</td>
<td>115 ± 10</td>
<td>266 ± 50</td>
<td>60 ± 4</td>
<td>4 ± 1</td>
<td>36 ± 4</td>
</tr>
<tr>
<td>ARC</td>
<td>50</td>
<td>38 (76)</td>
<td>110 ± 6</td>
<td>344 ± 42</td>
<td>50 ± 4</td>
<td>4 ± 0.7</td>
<td>46 ± 3</td>
</tr>
<tr>
<td>PGL</td>
<td>17</td>
<td>10 (59)</td>
<td>130 ± 10</td>
<td>312 ± 77</td>
<td>54 ± 8</td>
<td>4 ± 2</td>
<td>42 ± 8</td>
</tr>
<tr>
<td>SPC</td>
<td>24</td>
<td>15 (54)</td>
<td>105 ± 14</td>
<td>322 ± 115</td>
<td>56 ± 7</td>
<td>4 ± 2</td>
<td>40 ± 7</td>
</tr>
</tbody>
</table>

†% ± SE (range).
Table 2—Frequency and Degree of Alveolar Lymphocytosis Among Group B Patients without Respiratory Symptoms and with Normal Chest X-ray Film Findings

<table>
<thead>
<tr>
<th></th>
<th>OI</th>
<th>KS</th>
<th>ARC</th>
<th>PGL</th>
<th>SPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>5</td>
<td>14</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>No. of patients with lymphocytosis</td>
<td>2</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Mean lymphocytosis (%)</td>
<td>21 ± 2</td>
<td>39 ± 9</td>
<td>40 ± 6</td>
<td>26 ± 2</td>
<td>33 ± 11</td>
</tr>
<tr>
<td>in lymphocytic patients</td>
<td>(18-21)</td>
<td>(27-77)</td>
<td>(15-67)</td>
<td>(24-31)</td>
<td>(15-85)</td>
</tr>
</tbody>
</table>


15 percent of lymphocytes in lavage fluid. As shown in Table 1, we observed lymphocytic alveolitis in 45 percent (common bacterial infections) to 87 percent (extrapulmonary KS) of cases. This alveolitis was thus found in 78 percent of group A and 72 percent of group B patients. In those lymphocytic patients, the cellularity was increased in all subgroups (170 ± 32 to 344 ± 42 cells x 10^9/ml), with a mean lymphocytosis varying from 25 ± 3 percent (common bacterial infections) to 46 ± 3 percent (ARC) of cells in BAL fluid.

**Group A:** In AIDS patients with opportunistic infections, lymphocytosis (mean = 38 ± 2 percent) was found in 98 cases (85 percent of patients), 35 of them having more than 10 percent of polymorphonuclear cells (PMC). Among the 18 other cases without lymphocytosis, 13 had such a PMC excess in lavage fluid (data not shown). Of note is that absolute numbers of lymphocytes were extremely variable owing to the variability of cellularity (120 to 2,270 x 10^9 cells/ml).

In patients with common bacterial infections, the relative decrease of alveolar lymphocytes was due to the increase of percentage of PMC. Nevertheless, 45 percent of these patients had lymphocytosis. Finally, five of seven patients with pulmonary tuberculosis and ten of 13 patients with bronchopulmonary KS also had lymphocytosis.

**Group B:** The same diagnostic procedures as those used in group A patients had negative results. Nevertheless, an alveolar lymphocytosis could be detected in 54 percent (SPC) to 87 percent (extrapulmonary KS) of cases (see Table 2): 63 of 91 non-AIDS patients (70 percent) presented with this alveolitis (40 ± 7 to 46 ± 3 percent of BAL fluid cells). As shown in Table 2, such an alveolitis was observed in 59 percent (27 of 46) asymptomatic patients (ie, without respiratory symptoms and abnormality of chest x-ray film).

**T-Lymphocyte Analysis**

To identify the nature of the alveolar lymphocytosis, the alveolar lymphoid subsets could be analyzed in 37

Table 3—T-Lymphocyte Analysis

<table>
<thead>
<tr>
<th>Finding, Patient No.</th>
<th>Chest X-ray</th>
<th>Cellularity × 10^9/ml</th>
<th>Lymphocytes, %</th>
<th>T3, %</th>
<th>T4, %</th>
<th>T8, %</th>
<th>T8D44, %</th>
<th>T8D44 T8, %</th>
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<tr>
<td>OI</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>DIO*</td>
<td>150</td>
<td>45</td>
<td>93</td>
<td>3</td>
<td>90</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>DIO</td>
<td>370</td>
<td>54</td>
<td>84</td>
<td>12</td>
<td>74</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>Extrapulmonary KS</td>
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<td></td>
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<td>3</td>
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<td>550</td>
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<td>21</td>
<td>68</td>
<td>53</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>DIO</td>
<td>210</td>
<td>77</td>
<td>92</td>
<td>10</td>
<td>82</td>
<td>78</td>
<td>95</td>
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<tr>
<td>ARC</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>DIO</td>
<td>1,010</td>
<td>81</td>
<td>84</td>
<td>6</td>
<td>89</td>
<td>64</td>
<td>72</td>
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<td>6</td>
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<td>7</td>
<td>DIO</td>
<td>490</td>
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<td>89</td>
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<td>80</td>
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<tr>
<td>8</td>
<td>DIO</td>
<td>455</td>
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<td>9</td>
<td>DIO</td>
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<td>82</td>
<td>6</td>
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<td>87</td>
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<td>90</td>
<td>86</td>
<td>95</td>
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<tr>
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<td>14</td>
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<td>290</td>
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<td>95</td>
<td>8</td>
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<td>90</td>
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<tr>
<td>15</td>
<td>DIO</td>
<td>320</td>
<td>75</td>
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<td>11</td>
<td>74</td>
<td>72</td>
<td>97</td>
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<td>16</td>
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<td>280</td>
<td>23</td>
<td>89</td>
<td>15</td>
<td>76</td>
<td>63</td>
<td>83</td>
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</table>

*DIO, diffuse interstitial opacities.

HIV-related Lymphocytic Alveolitis (Guillon et al)
patients using a single or two-color immunofluorescence staining. In group A, eight patients were studied. In all of them we could demonstrate a T lymphocyte alveolitis mainly composed of CD8+ cells (50 to 90 percent). Using the D44 moAb, which characterizes the CTLs within the CD8 subset,13 we performed a two-color FACS analysis in two patients (Table 3). In both the alveolar lymphocytes had the phenotype of CTLs: CD8+ D44+, as the lymphocytes encountered in the pleural fluid of patient 2 (pulmonary tuberculosis with pleuritis).

In group B, the alveolar lymphocyte phenotype was analyzed in 29 patients. A CD8+ lymphocytosis was observed in all cases (40 to 93 percent). We then realized a dual fluorescence analysis with the T8 and D44 moAbs of the BAL fluid cells in 16 patients. As shown in Table 3, all had a CD8+ T-lymphocyte alveolitis in which 72 to 99 percent of CD8+ cells were CTLs (D44+).

Evaluation of Respiratory Involvement in Group B

Since group B patients did not have proved lung infectious or tumor process, although they had a high incidence of alveolar lymphocytosis, we tried to correlate the clinical presentation with the presence and the importance of the lymphocytic alveolitis. We assessed the pulmonary function using the presence or absence of clinical symptoms, radiologic abnormalities, altered gas exchange, and of small airway obstructive disease. Results are shown in Table 4.

Dyspnea on exercise or cough were observed in 60 (SPC) to 70 percent (PGL, ARC) of subjects having a lymphocytic alveolitis. Nevertheless, such alveolitis could be asymptomatic, since it was observed in 59 percent group B asymptomatic patients (see Table 2). Those latter patients had significantly milder lymphocytosis (p<0.01) than that of symptomatic patients. Finally, respiratory symptoms were almost constantly observed when the lymphocytosis was greater than 50 percent of BAL fluid cells.

Diffuse interstitial opacities (DIO) were observed in 32 cases (36 percent of lymphocytic patients). These patients had more lymphocytes in their BAL fluid than those with normal chest roentgenogram (45.5 ± 5 vs 25.4 ± 2, p<0.001). The DIO were associated with cough or dyspnea in 90 percent of cases and with hypoxemia in 80 percent of cases.

Arterial oxygen tension (PaO2) was highly variable, and a mild to severe hypoxemia was encountered in 30 to 40 percent of lymphocytic patients, especially in those with DIO.

Pulmonary function tests revealed abnormality of gas exchange (defined as a decrease of diffusing capacity for carbon monoxide or an increase of alveolar-arterial difference in oxygen tension on exercise) in 85 percent of the 33 patients tested. In eight patients we also observed a small airway obstruction (defined as forced expired flow at 25 percent of forced vital capacity <50 percent predicted). Nevertheless, in five patients presenting with a mild- to high-intensity lymphocytic alveolitis, but without respiratory symptom, all tests failed to reveal an abnormality, even in two cases with a moderate radiologic infiltration.

We thus observed a wide range of abnormalities, from the completely asymptomatic individual with a mild-intensity alveolitis, a normal chest x-ray film, and minor abnormalities in pulmonary function test to some patients with a severe exercise dyspnea, a dry cough, a high-intensity lymphocytic alveolitis, DIO, hypoxemia, major abnormalities of gas exchange, and, in a few cases, small airway obstruction.

Furthermore, an open lung biopsy (OLB) was performed in six group A patients (Kaposi sarcoma in five cases, P carinii in one case) and in four group B patients. In those latter patients, we demonstrated a diffuse infiltration involving lymphatic vascular channels and sparing the alveolar septa. A bronchiolitis was observed in three cases. The T-lymphocyte analysis performed on biopsy sections revealed a CD8+ infiltration in all cases.

### Table 4—Evaluation of Pulmonary Involvement in Group B Patients With Alveolar Lymphocytosis

<table>
<thead>
<tr>
<th>OI</th>
<th>KS</th>
<th>ARC</th>
<th>PGL</th>
<th>SPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>5</td>
<td>20</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Symptomics, N (%)</td>
<td>3 (60)</td>
<td>13 (65)</td>
<td>27 (70)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>DIO*, N (%)</td>
<td>1 (20)</td>
<td>9 (45)</td>
<td>12 (32)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>PaO2† (mean ± SE)</td>
<td>78 ± 5</td>
<td>88 ± 3</td>
<td>85 ± 4</td>
<td>83 ± 3</td>
</tr>
</tbody>
</table>

Pulmonary function tests‡

- Patients tested, N
- Dsb
- P(A-a)O2
- FEF25
- All tests normal

<p>| | | | | |</p>
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*DIO: diffuse interstitial opacities.
†mm Hg.
‡Results are expressed as number of patients with abnormal results compared with predicted values. Dsb: diffusing capacity for carbon monoxide; P(A-a)O2: alveolar-arterial difference in oxygen tension on exercise; FEF25: forced expired flow at 25% of forced vital capacity.
**DISCUSSION**

We undertook this prospective open study to investigate the frequency, the degree, and the clinical presentation of the HIV-related lymphocytic alveolitis in different stages of HIV disease. As already noted,5-9,16-18 HIV-infected patients as a group had a striking increase of lymphocytes in their BAL fluid, but the most important finding reported is that this alveolitis could be observed in 72 percent of patients with no evidence of previous or concomitant lung infection or tumor. The significance of such an alveolitis must be interpreted according to the nature of the underlying pulmonary status.

Group A patients were heterogeneous, and a lymphocytosis was found in 78 percent of cases. It seems difficult to delineate what is due to the pulmonary disease and what is possibly due to HIV infection. It has been shown19 that the high frequency of such alveolitis was also observed in other immunosuppressed patients with the same opportunistic infections. Thus, we cannot exclude the possibility that the lymphocytosis was, for instance, partially or exclusively a common response to a *P carinii* infection. However, 12 of these patients had a second BAL two to six months after the initial episode, and all of them showed a persistent lymphocytosis without detectable *P carinii* cysts (data not shown). In patients with common bacterial infections, the PMC excess in BAL fluid was expected, but in this setting lymphocytosis is more difficult to explain. These patients were very heterogeneous considering HIV disease stage. We suggest that this lymphocytic alveolitis could be related to HIV infection and independent of usual infection episodes.

In group B patients, particularly in non-AIDS patients, the existence of a lymphocytic alveolitis raised many questions. All diagnostic procedures, including OLB for four patients, had negative results. However, we cannot completely exclude some viral agent such as Epstein-Barr virus, which has been incriminated in an HIV-positive child with lymphocytic interstitial pneumonitis (LIP),20-22 or even Cytomegalovirus. Nevertheless, the homogeneity of our results and the number of patients make unlikely a failure of the diagnostic procedures. Finally, we could not avoid a bias (minor respiratory symptoms or abnormal chest x-ray film), and our patients may not reflect the entire HIV-positive population. Our data thus suggest an early lung involvement during HIV disease. One recent study23 indicated that persons with asymptomatic HIV infection may have incipient CNS involvement. Therefore, subtle symptoms concerning various organs can occur early in the natural history of this viral disease, even if the pathogenesis of such involvement are different.

The cell surface phenotype of the alveolar lymphocytes was predominantly CD8+ in the 37 patients tested from both groups A and B, a finding in conjunction with previous observations.6,7,18,24 A dual fluorescence analysis in 18 subjects belonging to different subgroups revealed in all cases that BAL fluid lymphocytes were composed of a large majority of cells double positive for the CD8 and D44 markers that identify the CTLs within the CD8 subset. In 14 of these patients, we demonstrated elsewhere25-27 that this T cell cytotoxic alveolitis was associated with HIV gag proteins bearing CD4+ alveolar macrophages whose HIV infection was confirmed by Southern blot analysis. We could also demonstrate that the alveolar lymphocytes of six of our patients (one AIDS, two ARC, one PGL, and two SPC) recognized and killed HIV-infected alveolar macrophages in vitro in an HLA-restricted fashion.27 Thus, these data suggest that CD8-positive T lymphocytes with cytotoxic activities are present in BAL fluid and might induce a local inflammation in the lungs by their interactions with HIV-proteins bearing alveolar macrophages. The coexistence of CTLs and HIV-infected alveolar macrophages raised two questions: first, is this immunologic conflict responsible for some effects on the alveolar structures, as suggested by the abnormalities of gas exchange? Second, are these macrophages functional? Indeed, in our series, we observed a very high incidence of bacterial pneumonia or bronchitis,28 which agrees with recent reports in the literature.29,30 These macrophages would thus serve not only as a reservoir for the HIV31 but also as dysfunctional cells, opening the way for infections of the lungs. Whether this alveolitis is related to the appearance of opportunistic infections, ie, AIDS, remains to be determined.

From a clinical point of view, the intensity of the lymphocytic alveolitis seems to be correlated with the existence of respiratory symptoms, pulmonary function test abnormalities, and diffuse interstitial opacities. In four patients, OLB disclosed a diffuse lymphocytic infiltration along lymphocytic vascular channels, very reminiscent of those seen in lymphocytic interstitial pneumonitis (LIP) as described by Carrington and Liebow,32 although sparing the alveolar septa. Noninfectious or nontumor lung involvement are frequently reported in HIV-infected patients: LIP has been described in children33-35 and also in adults with AIDS or ARC.24,36-40 LIP is usually associated with respiratory symptoms, a restrictive pattern in functional tests, and repeated usual infectious episodes, but it does not seem to represent a risk factor for progression to AIDS. Histologic features of LIP are diffuse infiltration of alveolar septa and peribronchial areas by lymphocytes and presence of nodular aggregates of lymphoid cells,33,41 no fibrosis is seen. A similar lymphocytic infiltration of other organs such as liver, kidney, or nerves is frequently associated.35,38,42 A few
patients have been treated with steroids, but the indication for such a treatment must be specified.

Spencer has described in non-HIV-infected patients an unusual entity that he refers to as pulmonary lymphoid hyperplasia (PLH). Similar observations have been made in AIDS and ARC patients. PLH is characterized by peribronchial nodular lymphoid aggregates and lymphoid infiltration involving lymphatic vascular channels but sparing alveolar septa. Clinical presentation does not differ from that of LIP. Yousem et al. described HIV-positive patients with overlapping features: follicular bronchitis/bronchiolitis associated with lymphoid hyperplasia; one of our patients, described elsewhere, presented with similar lesions. The involvement of bronchioles may explain the small airway obstructive disease that we found in some patients. Finally, several studies have reported on HIV-infected patients with nonspecific interstitial pneumonitis. Clinical presentation was quite diverse and often indistinguishable from that of opportunistic infections. Cytologic examination was not detailed, but OLB showed interstitial infiltration with lymphocytes and plasma cells; the exact localization of this infiltration was not specified. These patients could probably be included in the HIV-related PLH/LIP complex. We only performed OLB when the presentation was severe without a precise diagnosis, so we do not know the histologic features in patients with a mild-intensity lymphocytic alveolitis. But we suggest, as did Joshi and Oleske, that a continuum or spectrum of pulmonary lymphoid lesions exists during HIV disease, from lymphocytic alveolitis to severe lymphoid hyperplasia, with the LIP at the end of the spectrum. Those lymphocytic patients may have a particular form of respiratory involvement. In fact, we know that HIV can be isolated from BAL fluid and may infect alveolar macrophages. Lymphocytosis may then reflect the local expansion of a lymphocyte cytotoxic subset at the site of the viral disease activity. Thus, it may be possible that the lymphocytic alveolitis, with mild to severe histologic lesions, is an index reflecting the activity of HIV infection and the host reaction to it.

Lymphocytic alveolitis seems to be common in HIV-infected patients. Such an alveolitis was found in 70 percent of non-AIDS patients without detectable lung infectious or tumor processes. It may be asymptomatic but is more often associated with respiratory symptoms. Some patients had a severe presentation, particularly those with a high lymphocytosis and diffuse interstitial opacities, who can probably be included in the HIV-related PLH/LIP complex. In the 37 patients tested, belonging to different HIV disease stages, this alveolitis was composed of CD8-positive T-lymphocytes. We could demonstrate in 18 patients that these cells are cytotoxic and can be directed against HIV-infected or p18-bearing alveolar macrophages. This lymphocytic alveolitis could be related to a high frequency of usual infections, but as to opportunistic infections, this relation remains to be determined. Follow-up studies are in progress in our laboratories to determine whether it could be considered a prognostic index and whether a therapeutic regimen should be used.

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