Improvement of Symptomatic Human Immunodeficiency Virus–Related Lymphoid Interstitial Pneumonia in Patients Receiving Highly Active Antiretroviral Therapy

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To analyze the impact of highly active antiretroviral therapy on lymphoid interstitial pneumonia (LIP), we reviewed the medical files of 5 human immunodeficiency virus (HIV)–infected patients in whom LIP was diagnosed during 1996–2001 who had never previously received antiretroviral treatment. Patients were mildly immunosuppressed at the time of diagnosis of LIP but had high plasma HIV loads and marked circulating and pulmonary CD8 hyperlymphocytosis. All patients improved clinically, radiologically, and functionally; improvement was accompanied by a drastic reduction in the virus load and an increase in the CD4 lymphocyte count.

Interstitial pulmonary disease is common during the course of HIV infection and is usually caused by opportunistic pathogens or neoplasms [1]. Lymphoid interstitial pneumonia (LIP) is rare and usually occurs in children. It is characterized by diffuse lymphoid infiltration of the alveolar septa along lymphatic vessels [2], mainly by CD8 T lymphocytes and plasmocytes [3, 4]. It has been postulated that the lymphocyte infiltrate is a reaction to pulmonary infection by HIV and/or Epstein-Barr virus [3, 4]. LIP is most often asymptomatic but can cause fever, respiratory symptoms, and, occasionally, respiratory distress [4–7]. There has been no consistently effective treatment, although corticosteroid therapy has been shown to have variable efficacy in symptomatic patients [4–7]. We describe 5 cases of symptomatic LIP in HIV-infected adults, all of whom improved rapidly when they initiated HAART.

Patients and methods. The medical files of HIV-infected patients in whom LIP was diagnosed during the period of 1996–2001 were identified from the admission register of the chest unit at Hôpital Tenon (Paris). LIP was diagnosed on the basis of the following criteria [4]: (1) radiological signs of interstitial pneumonia; (2) CD8 hyperlymphocytosis (i.e., CD8 cells constituting >30% of the total lymphocyte count), as determined by examination of bronchioloalveolar lavage (BAL) specimens, and/or lymphoid infiltration (mostly involving T lymphocytes and plasma cells) of the lung parenchyma with predominantly alveolar septal and peribronchial distribution, as revealed by conventional histological examination; (3) absence of a causal pathogen (especially Pneumocystis carinii, cytomegalovirus [CMV], and mycobacteria); and (4) absence of lymphoma or lung disease resulting from drug hypersensitivity or environmental factors. Only patients who had never previously received antiretroviral treatment, who were not treated with corticosteroids or antibiotics, and who were observed for >6 months were included in this study. The cutoff date for this analysis was September 2002.

A standard form was used by the same physician (V.D.) to record the characteristics of the patients from the medical files. It comprised the following: (1) epidemiological characteristics; (2) characteristics of HIV infection, including circulating CD4 and CD8 lymphocyte counts and plasma HIV loads (as determined using the Chiron Quantiplex bDNA kit; detection limit, 50 copies/mL) and antiretroviral treatment received (1-, 2- or 3-drug regimen); (3) pulmonary and extrapulmonary signs and symptoms of LIP at hospital admission, including serum γ-globulin and lactic dehydrogenase levels, pulmonary function test (PFT) results, blood gases on room air and the diffusing capacity of the lung for carbon monoxide (DLCO), findings of thoracic imaging (standard radiography and CT with millimetric slices), findings of bronchial endoscopy with sample analysis (BAL and bronchial and transbronchial biopsies); and (4) LIP outcome data and immunologic and virologic status.

Values are expressed as means ± SEM or as medians and ranges. Differences were analyzed using the Mann-Whitney U test or the Wilcoxon matched paired test. P < .05 was considered to be statistically significant.

Results. Seven HIV-seropositive adults with diffuse interstitial lung disease who underwent investigations in the Hôpital Tenon chest unit during 1996–2001 had a final diagnosis of
LIP. Two of these 7 patients were excluded from this study because of inadequate follow-up. Characteristics of the patients are listed in table 1. Only 1 patient was a smoker. The risk factor for HIV infection was heterosexual intercourse for 3 patients, homosexual intercourse for 1 patient, and unknown for 1 patient.

All but 1 patient presented with LIP as the initial manifestation of HIV disease. The remaining patient (patient 1) already had a diagnosis of AIDS (cutaneous Kaposi sarcoma), but the CD4 cell count was >500 cells/mm³ at the time of admission to the hospital. None of the patients were receiving prophylaxis for P. carinii pneumonia or any other treatment with known pulmonary toxicity. The median CD4 cell count at the time of diagnosis of LIP was 269 cells/mm³ (range, 39–730 cells/mm³), or 16% (range, 5%–29%); the median CD8 cell count was 1204 cells/mm³ (range, 505–3015 cells/mm³), or 63% (range, 39%–80%). The median plasma virus load at the time of LIP diagnosis was 92,000 copies/mL (range, 70,000–340,000 copies/mL).

All of the patients had respiratory symptoms and/or general signs or fever that started an average of 3 months before hospital admission (range, 1–12 months; table 1). In 2 patients, LIP was discovered in the context of a pulmonary infection (bronchitis and pneumonia; patients 2 and 4, respectively). One patient (patient 5) had constrictive retrosternal pain subsequently attributed to cardiomyopathy due to myocardial lymphoid infiltration. Two had sicca syndrome. Physical examination revealed peripheral adenopathy in 3 patients and hepatosplenomegaly in 2 patients. All of the patients had polyclonal hypergammaglobulinemia (γ-globulin level, 26–70 g/L). The lactic dehydrogenase level was normal in 3 patients and elevated (1.5 times the upper limit of normal) in 2 patients.

Only 1 patient’s (patient 3) radiographs revealed nothing abnormal; for the other 4 patients, radiography revealed micronodular interstitial syndrome, together with areas of alveolar condensation in 1 patient (patient 4). For all patients, CT of the chest revealed abnormalities (table 1). CT also revealed expiratory trapping evocative of bronchiolitis in one patient (patient 2) and nonnecrotic mediastinal adenopathies in another patient (patient 5). CT revealed no cysts or pleural effusion. PFT results were normal for 4 patients and revealed a restrictive syndrome with a reduction in total lung capacity in 1 patient (patient 5). The levels of partial pressure of oxygen, arterial (PaO₂), in room air were moderately low (range, 50–85 mm Hg), and the DLCO always decreased (28%–65% of the predicted values; table 1).

Bronchial endoscopy was performed for every patient, and no endobronchial abnormalities were found. Examination of BAL specimens revealed marked hypercellularity, with a median cell count of 750 × 10⁶ cells/mL (range, 620–2100 × 10⁶ cells/mL), mainly consisting of lymphocytes (60%–88%) with the CD8 phenotype (82%–92%). In each patient, the percentage of CD8 lymphocytes was higher in BAL fluid than in peripheral blood (P < .05 for BAL vs. blood; data not shown), suggesting recruitment of these cells to the lungs. No pathogens were found by specific direct examination and culture for bacteria, viruses other than HIV, and fungi. For all patients, the diagnosis of LIP was confirmed by histological analysis of transbronchial biopsy specimens.

All 5 patients were alive at the cutoff date for this analysis (September 2002), with a mean duration of follow-up of 40 months after LIP diagnosis (range, 18–67 months). None had opportunistic infections during follow-up, but 1 patient had recurrent bronchitis and 1 had bacterial pneumonia (no microbiological documentation). All patients received antiretroviral treatment, which started 1–3 months after the diagnosis of LIP and consisted of either a 3-drug regimen from the outset (2 nucleoside analogues and 1 protease inhibitor; patients 1

Table 1. Main characteristics of HIV-infected patients with lymphoid interstitial pneumonia at the time of admission to the hospital and during follow-up.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age in years</th>
<th>Race</th>
<th>Characteristics at hospital admission</th>
<th>Characteristics at 6 months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
<td>CT scan finding(s)</td>
</tr>
<tr>
<td>1</td>
<td>M, 53</td>
<td>White</td>
<td>Cough, dyspnea, fever, sicca syndrome</td>
<td>ggo</td>
</tr>
<tr>
<td>2</td>
<td>F, 34</td>
<td>Black</td>
<td>Cough, dyspnea, fever</td>
<td>ggo, mn</td>
</tr>
<tr>
<td>3</td>
<td>M, 64</td>
<td>White</td>
<td>Cough, dyspnea, weight loss, sicca syndrome</td>
<td>ggo</td>
</tr>
<tr>
<td>4</td>
<td>F, 24</td>
<td>Black</td>
<td>Cough, dyspnea</td>
<td>ggo, mn, ao, ln</td>
</tr>
<tr>
<td>5</td>
<td>M, 32</td>
<td>Black</td>
<td>Cough, dyspnea, weight loss, thoracic pain</td>
<td>ggo</td>
</tr>
</tbody>
</table>

NOTE. ao, Alveolar opacity; DLCO, diffusing capacity of the lung for carbon monoxide; ggo, ground-glass opacity; ln, lymph nodes; mn, micronodules; NA, not available; PaO₂, partial pressure of oxygen, arterial.

* PaO₂ was measured in room air.

** DLCO is expressed as a percentage of the normal value.
and 3–5) or 2 nucleoside analogues, to which a protease inhibitor was added later (patient 2).

All of the patients improved clinically, with a reduction (patients 1 and 5) or disappearance (patients 2–4) of symptoms and general signs after an average of 3.5 months of antiretroviral treatment (range, 1–6 months; table 1). This was accompanied by an improvement in chest image findings and/or PFT results obtained after 6–8 months of antiretroviral treatment. Resting $\text{Pa}_2$ ($n = 5$) and DLCO ($n = 4$) values improved in every patient tested (table 1). Chest radiograph and/or CT findings normalized in the 4 patients who received a 3-drug regimen from the outset, whereas the findings only improved in the patient who initially received 2 nucleoside analogues (patient 2; table 1). None of the patients experienced relapse, and none had conditions that progressed to fibrosis or lymphoma.

The HIV load decreased in all of the patients concomitantly with the clinical improvement after an average of 3.6 months of antiretroviral treatment (range, 15 days to 6 months). The virus load became undetectable (i.e., <50 copies/mL) in 3 patients ($P < .05$ for before vs. after the initiation of HAART; data not shown). The CD4 cell count increased in all patients, reaching a median of 359 cells/mm$^3$ after 6 months (range, 228–781 cells/mm$^3$; 22% of total T cells [range, 17%–28%]; $P < .05$ for before vs. after the introduction of HAART; data not shown), whereas the CD8 T cell count remained unchanged, with a median level of 1519 cells/mm$^3$ at 6 months (range, 901–3730 cells/mm$^3$; 60% of total T cells [range, 47%–70%]; $P = .05$ for before vs. after the introduction of HAART; data not shown). These findings were confirmed after long-term follow-up (range, 18–67 months).

**Discussion.** We describe 5 typical cases of LIP occurring in HIV-seropositive adults, all of whom improved when they received HAART. All patients had subacute diffuse pulmonary infiltration with ground-glass opacities visible on thoracic CT scans as well as decreases in the DLCO value and/or resting hypoxemia associated with lymphocytic alveolitis (mainly CD8 T cells), as assessed by examination of BAL specimens; histological confirmation was obtained for all cases. Pulmonary infections ($P. carinii$, mycobacteria, and CMV) were ruled out by direct examination and culture of blood and respiratory samples. As previously reported [5–8], most of our patients were of African origin, and all had mild immunosuppression. The lymphoid hyperplasia characteristic of LIP [6, 9] affected organs other than the lungs in our patients (sica syndrome, peripheral adenopathy, hepatosplenomegaly, or myocardial involvement), and polyclonal hypergammaglobulinemia was also observed, reflecting nonspecific polyclonal B cell stimulation [6].

Some authors consider LIP to result from an exaggerated cellular immune response to HIV in patients with intense HIV replication and/or pulmonary Epstein-Barr virus reactivation [3, 4]. Indeed, the pulmonary virus load is higher in patients with LIP than in asymptomatic patients at a given stage of HIV-related immunosuppression [4, 10]. Likewise, in mice transgenic for HIV-1 genes, the severity of LIP-associated histological lesions and clinical manifestations correlates with the level of tissue viral load [11]. Our patients had only moderate immunosuppression, but all had elevated plasma virus loads associated with pulmonary recruitment of CD8 lymphocytes, probably of the cytotoxic phenotype, as we have demonstrated elsewhere [12–14].

The natural history of LIP is variable, and without treatment, the clinical course may deteriorate, remain stable, or even improve [4–7]. However, because LIP-related respiratory symptoms or fever began 1–12 months before diagnosis, and because HAART was initiated 1–3 months after the diagnosis of LIP was made, the hypothesis of a spontaneous improvement in LIP in our patients seemed improbable. There are few data on the efficacy of antiretroviral drugs in HIV-infected patients with LIP. Zidovudine monotherapy has shown inconsistent efficacy in these patients [7, 15, 16]. Two studies involving 13 children and 1 adult showed clinical, radiological, and functional improvements associated with receipt of a 3-drug antiretroviral regimen [17, 18]. The improvement in LIP observed in our patients receiving HAART, together with the significant increase in the CD4 cell count, may have resulted from the immune reconstitution described in association with HAART [1]. This is unlikely, however, because this immune reconstitution is associated with an improved response to HIV mediated by cytotoxic CD8 lymphocytes, which may paradoxically aggravate histological lesions, as demonstrated for other latent and/or active viral infections, such as CMV infection and hepatitis B or C virus infection [19, 20]. The improvement in LIP is more likely to have resulted from the reduced HIV load in the lungs, concomitant with the drastic reduction in the plasma virus load. Indeed, the reduction in the pulmonary virus load might lead to recirculation of CD8 lymphocytes that were sequestrated in the lungs, as has recently been described in lymphoid organs [21], thereby reducing the lymphocytic alveolitis and its deleterious effects on the alveolocapillary membrane [14]. Unfortunately, the iterative evaluation of pulmonary virus load in our patients did not allow us to test this hypothesis.

**References**

4. Travis WD, Fox CH, Devaney KO, et al. Lymphoid pneumonitis in 50 adult patients infected with the human immunodeficiency virus: lym-


