Upper Respiratory Tract Involvement in the Course of Diffuse Infiltrative Lymphocytosis Syndrome in HIV-1–Infected Patients: Report of 2 Cases

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Diffuse infiltrative lymphocytosis syndrome (DILS) in patients with human immunodeficiency virus (HIV) infection is characterized by persistent CD8+ lymphocytosis with visceral lymphocytic infiltration. DILS induces a large spectrum of clinical features. We describe 2 HIV-infected patients with upper respiratory tract involvement that occurred during the course of DILS.

Diffuse infiltrative lymphocytosis syndrome (DILS) in HIV-infected patients is characterized by persistent CD8+ lymphocytosis with visceral lymphocytic infiltration located mostly in the salivary glands. It causes gland enlargement, dry eyes, and dry mouth. Histopathological findings confirm the diagnosis, revealing lymphocytic infiltration in the salivary or lacrimal glands without granulomatous or neoplastic involvement. However, there is a spectrum of disease that does not meet the classic definition of DILS. We describe 2 HIV-infected patients who had DILS with upper respiratory tract involvement and rhinitis with nasal crusting.

Patient 1. A 24-year-old woman from the Democratic Republic of the Congo presented to the hospital with a 3-month history of myalgia, muscle weakness, weight loss, and dyspnea. Clinical examination revealed proximal muscle weakness (with a score of 4–5 on the Medical Research Council scale), xerostomia, xerophthalmia, nasal crusting, and obstruction. Sicca symptoms had been evolving for 8 months. There was no parotid gland enlargement. Anterior rhinoscopic examination showed mild rhinitis with nasal crusting. Lung auscultation revealed crackles. Serologic analysis revealed a positive HIV-1 titer, with a CD4+ cell count of 152 cells/mm3 (9% of the total cell count), a CD8+ cell count of 1070 cells/mm3 (normal range, 300–1000 cells/mm3; 64% of the total cell count), and a HIV RNA load of 271,000 copies/mL (Amplicor Monitor, version 1.5 [Roche]). The creatine kinase concentration was 1500 UI/L (normal level, <265 UI/L), the aspartate aminotransferase level was 106 UI/L (normal level, <56 UI/L), the lactate dehydrogenase level was 914 UI/L (normal level, <350 UI/L), and the aldolase level was 11 UI/L (normal level, <7 UI/L). Chest radiography and thoracic CT showed diffuse micronodular interstitial infiltrates. Pulmonary function testing demonstrated a restrictive pattern (forced vital capacity, 52% of the expected value) and abnormal gas exchange (single-breath carbon monoxide diffusing capacity, 15% of the expected value). Analysis of a bronchoalveolar lavage specimen revealed 750,000 cells/mL, of which 85% were lymphocytes (90% CD8+ cells). Gram, acid-fast, and Grocott stains showed no organisms, and results of culture for opportunistic pathogens were negative. Immunological analysis revealed a positive anti-DNA antibody titer (1:320) and positive results of a Farr assay (12 UI; normal value, <7 UI/L), but results of other immunological tests were negative (table 1). Electromyographic exploration showed myopathic features with alteration of motor units and fibrillations without abnormal neurologic conduction. MRI of muscles showed a diffuse bilateral hypersignal. Quadriceps muscle biopsy showed numerous foci of endomyosial and, to a lesser extent, perimysial inflammation. Infiltrates were mainly comprised of CD8+ lymphocytes, suggestive of polymyositis. Results of p24 immunohistochemical analysis were negative. No granulomatous inflammation or pathogens were detected. There was no sign of neoplasia. Minor salivary gland biopsy showed grade 4 lymphocytic sialadenitis, as determined by the method of Greenspan and Daniels [1], comprised of plasmacytes and CD8+ T cells (figure 1).

Antiretroviral treatment (tenofovir, lamivudine, lopinavir, and ritonavir) without steroid therapy was introduced, resulting in rapid clinical improvement. After 6 months of treatment, no muscular signs or dyspnea were found. Findings of nasal examination were normal. Thoracic CT findings were normal, and pulmonary function testing showed no abnormalities. The CD4+ cell count was 258 cells/mm³, the HIV load was <50 copies/mL, and the creatinine kinase concentration was 244 UI/L.

Patient 2. A 27-year-old woman from Mali presented with a 1-year history of dyspnea, cough, dysphonia, and xerostomia.
Table 1. Clinical, laboratory, and immunological parameters for 2 HIV-infected patients with diffuse infiltrative lymphocytosis syndrome.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td><strong>Clinical signs and symptoms</strong></td>
<td></td>
<td></td>
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<tr>
<td>Glandular</td>
<td>Xerostomia, xerophthalmia</td>
<td>Xerostomia, xerophthalmia</td>
</tr>
<tr>
<td>Extraglandular</td>
<td>Lymphocytic interstitial pneumonia, myositis, rhinitis with nasal crusting</td>
<td>Lymphocytic interstitial pneumonia, vocal cord edema, crusted rhinitis</td>
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<tr>
<td><strong>Laboratory finding</strong></td>
<td></td>
<td></td>
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<tr>
<td>CD4+ cell count, cells/mm$^3$ (% of total cell count)</td>
<td>152 (9)</td>
<td>140 (4)</td>
</tr>
<tr>
<td>CD8+ cell count, cells/mm$^3$ (% of total cell count)</td>
<td>1070 (64)</td>
<td>2600 (74)</td>
</tr>
<tr>
<td>HIV-RNA load, copies/mL</td>
<td>271,000</td>
<td>250,000</td>
</tr>
<tr>
<td><strong>Immunological finding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody titer</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antinuclear antibody titer</td>
<td>Positive (1:320)</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-DNA antibody</td>
<td>Positive (152 UI/mL)</td>
<td>Negative (c&lt;7 UI)</td>
</tr>
<tr>
<td>Farr assay</td>
<td>Positive (12 UI)</td>
<td>Negative</td>
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<tr>
<td>Anti-Ro antibody titer</td>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td>Anti-La antibody titer</td>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td>Anti–Jo-1 antibody titer</td>
<td>Negative</td>
<td>Negative</td>
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Clinical examination revealed cervical, axillary, and inguinal lymphadenopathies, fine lung crackles, and rhinitis with nasal crusting. Nasal endoscopy showed severe bilateral rhinitis with nasal crusting, with edema and ulcerations in the nasal mucosa. Laryngeal endoscopy revealed right vocal cord thickening and inflammation. Serologic analysis revealed a positive HIV-1 titer, with a CD4+ cell count of 140 cells/mm$^3$ (4% of the total cell count), a CD8+ cell count of 2600 cells/mm$^3$ (74% of the total cell count), and a HIV RNA load of 250,000 copies/mL. Chest radiography and thoracic CT revealed diffuse interstitial infiltrates. Pulmonary function tests showed decreased carbon monoxide diffusion (35% of the expected value). Examination of a bronchoalveolar lavage specimen revealed 150,000 cells/mL, 58% of which were macrophages and 39% of which were lymphocytes (93% CD8+ cells). Findings of direct examination were normal, and results of culture for pathogens were negative. Histologic examination of a nasal biopsy specimen revealed ulceration with intense lymphocytic infiltration, mainly comprised of CD8+ lymphocytes (figure 2). No vasculitis, granulomatous inflammation, or pathogens were detected. Bronchial biopsy showed the same pattern of intense CD8+ T cell inflammation as that found in patient 1, with no sign of neoplasia. Minor salivary gland biopsy showed a grade 3 lymphocytic sialadenitis, as determined by the method of Greenspan and Daniels, comprised of plasmacytes and CD8+ T cells (figure 3). Results of immunological tests were negative, and the levels of complement and angiotensin conversion enzyme were normal (table 1).

Treatment was initiated with antiretroviral agents (didanosine, zidovudine, indinavir, and ritonavir) and steroids (prednisone, 1 mg/kg per day). The patient was lost to follow-up.

**Discussion.** We describe a diffuse CD8+ lymphocytosis syndrome in 2 HIV-infected patients that induced an unusual clinical manifestation, including rhinitis with nasal crusting. The diagnosis of DILS in these patients was based on the presence of CD8+ lymphocytosis in conjunction with multivisceral infiltration of CD8+ lymphocytes, with lymphocytic interstitial pneumonia, focal sialadenitis, and polymyositis in one case (patient 1).

Some HIV-infected persons respond to HIV infection by developing a syndrome characterized by persistent circulating CD8+ lymphocytosis with visceral lymphocytic infiltration. DILS was first described by Solal-Celigny et al. [2] in 1985 and has been referred to as DILS since 1989 [3]. The diagnostic criteria proposed by Itescu and Winchester [4] require HIV seropositivity, bilateral salivary gland enlargement or xerostomia for >6 months, and histologic confirmation of salivary or lacrimal gland lymphocytic infiltration in the absence of granulomatous or neoplastic involvement. The diagnosis of DILS can be made on the basis of a labial salivary gland biopsy demonstrating a focal lymphocytic infiltrate with a predominance of CD8+ cells, in contrast to CD4+ cell–predominant infiltrates in persons with Sjögren syndrome. Minor salivary gland biopsies revealed grade 4 and 3 lymphocytic sialadenitis in patients 1 and 2, respectively, according to the method of Greenspan and Daniels, which was validated in a study of DILS.
Figure 1. Hematoxylin-eosin–stained salivary gland biopsy specimens obtained from patient 1 showing interstitial lymphoplasmacytic infiltrates (A; original magnification, ×25) and lymphoid infiltration within the intralobular salivary duct epithelium (B; original magnification, ×100). C, Inflammatory focus within the intralobular salivary duct epithelium, which was positive for anti-CD8+ antibody (original magnification, ×400). D, p24 Immunohistochemical analysis showing HIV-infected macrophages (original magnification, ×400).

by McArthur et al. [5]. Some authors consider that Ga67 scintigraphy revealing intense uptake of the tracer in the salivary glands eliminates the need for minor salivary gland biopsy [6, 7]. A significantly elevated mean total CD8+ lymphocyte count of 1639 cells/mm³ was observed often in the series reported by Kazi et al. [6]. The presence of infiltrating lymphocytes provided evidence that DILS represents major histocompatibility complex–restricted, antigen-driven oligoclonal selection of CD8+CD29+ lymphocytes.

The prevalence of DILS among HIV-infected persons varies from 0.8% to 7%, depending on diagnostic criteria and ethnicity [6–8]. A genetic predisposition to DILS has been suggested by the presence of HLA-DRB1, a subtype of HLA-DR5 alleles. The estimated relative risk for DILS conferred by HLA-DR5 among African Americans infected with HIV is 16.9% [6].

DILS usually presents as painless, often massive parotid enlargement accompanied by sicca symptoms (xerostomia and xerophthalmia). Enlargement of submandibular and lacrimal glands is also often present. Extraglandular features that are not associated with classic clinical diagnostic criteria can reveal DILS [2]. In a recent series, lungs were the most common extraglandular sites affected, inducing lymphocytic interstitial pneumonitis in 12 (31%) of 38 patients [6]. The lymphocytic infiltration may also cause peripheral neuropathy, hepatitis, interstitial nephritis, and myositis [6, 9].

HIV-related polymyositis has clinical and histopathological features resembling idiopathic polymyositis [10, 11]. Interstitial inflammatory infiltrates of CD8+ T cells and macrophages accompanied by degenerating and regenerating myofibrils are seen on light microscopy and are sometimes associated with perivascular infiltrates, which were particularly dense in patient 1 [11, 12]. HIV proviral DNA in muscle biopsy specimens is detected in lymphocytes but not within the muscle fibers, suggesting that HIV-associated polymyositis is not due to persistent...
Figure 2. Hematoxylin-eosin–stained nasal biopsy specimen obtained from patient 2 showing mucosal ulceration and intense lymphocytic inflammation (A; original magnification, ×25). Inflammatory cells were mainly comprised of CD8+ T cells, which infiltrated the epithelium, the lamina propria (B; original magnification, ×100) and the salivary glands (C; original magnification, ×400).

Figure 3. Hematoxylin-eosin–stained salivary gland biopsy specimens obtained from patient 2 showing one of the foci of lymphoplasmacytic infiltrates, with lymphoid infiltration within the intralobular salivary duct epithelium (A; original magnification, ×400) and the inflammatory focus and lymphocytes within the intralobular salivary duct epithelium, which was positive for anti-CD8+ antibody (B; original magnification, ×400).
infection of the muscle fiber by HIV [10, 13]. Our observation confirms that HIV-associated polymyositis can be a part of the spectrum of DILS.

Sinonasal involvement is a previously unrecognized manifestation of DILS. Both of our patients described sinonasal symptoms with rhinitis and nasal crusting, and one also had dysphonia with vocal inflammation. Rhinitis with nasal crusting was related to CD8⁺ lymphocytic infiltration with ductal hyperplasia on histologic examination of the nasal biopsy specimen obtained from patient 2. Nasal mucosal involvement may be more frequent than is clinically appreciated; uptake of Ga⁺⁺ at this site was reported by both Kazi et al. [6] and Itescu et al. [14]. Involvement of the upper respiratory tract has been described in the course of many systemic diseases, such as Wegener granulomatosis, sarcoidosis, and Sjögren syndrome [15], all of which were ruled out in our patients.

There are no good randomized studies comparing treatment modalities for DILS. When the standard of care for HIV infection was zidovudine monotherapy, several authors reported that antiretroviral treatment might be effective for treating glandular swelling, sicca symptoms, and visceral manifestations associated with DILS [4, 16]. However, there are no published data about the effect of HAART and protease inhibitor therapy. Severe visceral manifestations of DILS, such as lymphocytic interstitial pneumonia, may also require treatment with corticosteroids or immunosuppressive agents [12]. In our 2 cases, one patient received only HAART, resulting in a favorable outcome, and the other patient was lost to follow-up.

In persons without HIV infection, DILS usually involves salivary or lacrimal glands. However, in HIV-infected individuals, typical parotid gland enlargement may be absent, and the large spectrum of DILS, including upper respiratory tract involvement, may result in delayed or incorrect diagnosis. Histologic study is essential for diagnosis. HAART alone may be efficient for treating DILS.

Acknowledgments

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References