Lymphocytic alveolitis in primary HIV infection

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■ Primary infection with the human immunodeficiency virus (HIV-1) has been associated with a self-limited illness resembling acute infectious mononucleosis. Pulmonary manifestations have been notably absent in published reports. The authors describe a 28-year-old homosexual male who presented with primary HIV-1 infection associated with CD8+ lymphocytic alveolitis. Diagnosis was delayed because HIV antibody was not detected by the Abbott ELISA, although the same and subsequent specimens were later found to be positive by Genetic Systems' ELISA and Western blot analysis. Lymphocytic alveolitis must be added to the expanding clinical spectrum of acute HIV-1 infection. The time to detection of seroconversion may vary with different immunoassays.

□INDEX TERMS: ALVEOLITIS; HIV-1 □CLEVE CLIN J MED 1990; 57:379-382

PRIMARY INFECTION with the human immunodeficiency virus (HIV-1) has been associated with a self-limited illness that resembles acute infectious mononucleosis in up to 92% of seroconverting individuals.[1] Common symptoms include fever, lymphadenopathy, arthralgias, myalgias, headache, sore throat, diarrhea, and a truncal maculopapular rash. Pulmonary manifestations have been notably absent in previously reported patients with primary HIV-1 infection, except for a recently published case with interstitial pulmonary infiltrates.[2] Lymphocytic interstitial pneumonitis, alveolitis, and bronchiolitis have been described in patients with AIDS-related complex and AIDS,[3–6] and a CD8+ T lymphocytic alveolitis has been noted in asymptomatic individuals infected with HIV-1.[7] We report a case of primary HIV-1 infection associated with CD8+ lymphocytic alveolitis.

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CASE REPORT

In late April 1988 a previously healthy 28-year old homosexual male experienced fever to 39.5°C, sore throat, myalgias, anorexia, and a 20-pound weight loss. Symptoms persisted and in May 1988 he was hospitalized elsewhere. The physical examination was reportedly normal. The leukocyte count was 2.5×10^9/L with 0.60 lymphocytes, 0.33 granulocytes, and 0.05 bands. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were mildly elevated. Serologic studies for hepatitis A and hepatitis B were negative. A chest radiograph was normal. Serologic testing for HIV-1 antibodies by the Abbott ELISA was negative on May 19 and on June 6. Percutaneous liver biopsy demonstrated mild fatty infiltration. Splenomegaly was noted

TABLE 1
LABORATORY FINDINGS IN A 28-YEAR-OLD HOMOSEXUAL MAN WITH LYMPHOCYTIC ALVEOLITIS AND PRIMARY HIV INFECTION

	Date				
Test	5/19/88	6/6/88	6/9/88	7/1/88	8/1/88
ELISA (Abbott)*	–	–	+	ND	+
ELISA (Genetic Systems†)	+	+	+	ND	+
Western Blot	+‡	+	+§	ND	+
Serum p24 Antigen (DuPont)	+	+	–	ND	–
Room air ABG pH			7.50	7.42	
P_{O_2} (mm Hg)			73	94	
P_{CO_2} (mm Hg)			32	39	
DLCO % predicted			72	92	

D = Not done
* Patient/cut-off absorbance ratios: 5/19 = 0.81; 6/6 = 0.87; 6/9 = 5.74; 8/1 = >12.
† Patient/cut-off absorbance ratios: 5/19 = 5.05; 6/6 = 9.05; 6/9 = 9.40; 8/1 = 8.55.
‡ Western blot (DuPont/Biotech) bands of varying intensity at p24, p51, p55, p66, and gp120/160.
§ First appearance of band at pg41.

on computerized tomography of the abdomen. The patient's fever persisted for the next 2 weeks and an unproductive cough developed, with mild dyspnea on exertion. A diagnosis of viral upper respiratory tract infection was made and the patient was discharged. He presented to the Cleveland Clinic on June 8 for further evaluation.

On examination he was in mild respiratory distress. His temperature was 37.5°C and respirations were 24 per minute. Blood pressure and pulse were normal. The liver was palpable 1 cm below the right costal margin with a span of 8 cm. The spleen tip was palpable at the left costal margin. There was no adenopathy.

The leukocyte count was 11×10^9/L with 0.29 neutrophils, 0.01 bands, 0.42 lymphocytes, 0.18 reactive lymphocytes, and 0.10 monocytes. Hemoglobin was 138 g/L and the platelet count was 114×10^9/L. AST was 1.45 ukat/L, alkaline phosphatase 2.44 ukat/L, LDH 6.41 ukat/L, and bilirubin 13.7 µmol/L. The rapid plasma reagin test for syphilis was nonreactive. Serologic tests for hepatitis A and B were negative.

Serologic testing for Epstein-Barr virus (EBV) produced the following results: EBV viral capsid antigen (VCA) IgM <1:10, EBV VCA IgG 1:320, EBV early antigen 1:80, EB nuclear antigen ≥1:8. Testing was negative for cytomegalovirus IgM; although testing was positive for cytomegalovirus IgG, a convalescent titer was unchanged. Acute and convalescent serologic testing for influenza A and B and parainfluenza 1, 2, and 3 were negative. Respiratory syncytial virus IgG was 1:512 by immunofluorescent antibody assay, but a convalescent titer was unchanged.

A chest radiograph demonstrated subtle prominence of interstitial markings. Measurement of arterial blood gases on room air revealed a pH of 7.50, pCO_2 of 32 mmHg, and pO_2 of 73 mmHg. The carbon monoxide diffusing capacity (DLCO) was 22.4 mL/m/mmHg, 72% of the predicted value. The CD4 count was 832 cells/µL (normal, 436 to 1,394); the CD8, 5,260 cells/µL (normal, 166 to 882); and the CD4/CD8 ratio 0.2. Fiberoptic bronchoscopy disclosed no anatomic abnormalities. Bronchoalveolar lavage (BAL) fluid contained 213×10^3 cells/mL with 0.53 lymphocytes, 0.02 monocytes, and 0.44 alveolar macrophages. Immunohistochemical analysis of recovered cells demonstrated a predominance of $CD8^+$ cells with no identifiable $CD4^+$ cells. Transbronchial biopsy revealed normal lung parenchyma. Special stains for *Pneumocystis carinii*, acid-fast bacilli, fungi, and viral inclusions were negative. Cultures for bacteria, mycobacteria, fungi, mycoplasma, adenovirus, cytomegalovirus, and herpes simplex virus were negative.

Serum specimens from May 19 and June 6, 1988, were obtained from the outside hospital. These were again negative for HIV-1 antibody by the Abbott ELISA, with patient/cut-off absorbance ratios of 0.81 and 0.87, respectively. The same specimens were positive for HIV-1 antibody by Genetic Systems' HIV ELISA. Both sera were positive for HIV-1 p24 antigen by the DuPont assay, and positive by Western blot analysis with bands at p24, gp120, and gp160. Subsequent sera, beginning June 9, were strongly positive for HIV-1 antibody by the Abbott ELISA, confirming seroconversion.

The patient's fever, constitutional symptoms, and respiratory complaints resolved and he was discharged. Two weeks later the spleen was no longer palpable. The DLCO was 92% of the predicted value and room air arterial blood gases were normal. The CD4 count remained normal at 661 cells/ µL, but the serum p24 antigen was negative on August 1 (*Table 1*). Cultures of peripheral blood mononuclear cells were positive for HIV-1. He has remained asymptomatic.

DISCUSSION

This patient demonstrated a lymphocytic alveolitis composed predominantly of $CD8^+$ cells in the setting of acute HIV-1 infection. The presence in the BAL fluid of 213×10^3 cells/mL with 53% lymphocytes is clearly ab-

normal. Normal values for BAL cellularity are 120 ± 50 × 10^3 cells/mL with a differential including 91 ± 4% macrophages, 1 ± 1% polymorphonuclear leukocytes, and 8 ± 3% lymphocytes.[7–9] Normal values for BAL lymphocyte subsets are 50 ± 10% $CD4^+$ cells and 30 ± 7% $CD8^+$ cells.[7] Although the transbronchial lung biopsy was normal, this may have been attributable to sampling error, given his subtle radiographic findings.

The earliest serum specimens were positive by Genetic Systems' HIV ELISA and by Western blot analysis; however, the patient exhibited self-limited HIV-1 p24 antigenemia and seroconversion with the Abbott ELISA, confirming primary HIV-1 infection. Moreover, HIV-1 was cultured from the patient's peripheral blood. Serologic studies for Epstein-Barr virus, cytomegalovirus, influenza A and B, respiratory syncytial virus, and parainfluenza 1, 2, and 3, and cultures of BAL fluid failed to disclose another identifiable infectious agent. We therefore believe that our patient's pulmonary symptoms and lymphocytic alveolitis were a manifestation of his primary HIV-1 infection.

Other reports have suggested that, in some patients, seroconversion to HIV-1 may be detected earlier by Western blot analysis or with one manufacturer's ELISA *v* that of another.[10] Our case illustrates this point and emphasizes the importance of serially testing patients who are suspected of having primary HIV-1 infection. Initial serum specimens may be negative for antibody, or may have antibodies present at concentrations below the sensitivity of a particular test. Such sera may be positive earlier by other tests, such as Western blot analysis or p24 antigen assay.

To our knowledge, this case represents the first published report of lymphocytic alveolitis associated with primary HIV-1 infection. A recent report described a 26-year-old female with primary HIV infection accompanied by interstitial pulmonary infiltrates.[2] Bronchoscopy was performed but cellular analysis of the BAL fluid was not reported and virus was not grown from lavage fluid. Aside from this case, pulmonary involvement has not been previously reported with primary HIV-1 infection.

Several investigators have examined the cellular composition of BAL fluid in patients with AIDS and AIDS-related complex (ARC).[7,11–15] In one recent study 85% of patients with AIDS or ARC had lymphocytic alveolitis, with a predominance of $CD8^+$ cells.[7] This same study examined asymptomatic patients infected with HIV-1 (without AIDS or ARC) and found $CD8^+$ lymphocytic alveolitis in 6 of 14.[7] None of these patients was described as having primary HIV infection. Pulmonary symptoms were almost invariably present when more than 50% of BAL fluid cells were lymphocytes, as occurred in our patient.[7]

The pathogenesis of the lymphocytic alveolitis in our case is unclear. We did not attempt to isolate HIV-1 from the BAL fluid. Other investigators have demonstrated the association of $CD8^+$ lymphocytic alveolitis in HIV-1 infection, with the presence of $CD4^+$ alveolar macrophages expressing HIV-1 gag proteins.[16,17] BAL-derived $CD8^+$ lymphocytes from such patients have been shown to kill HIV-1 infected alveolar macrophages in vitro. This suggests that cytotoxic activity of $CD8^+$ cells in vivo may produce a local inflammatory response in the lung by virtue of their interaction with HIV-infected alveolar macrophages. We did not attempt to identify $CD4^+$ HIV-infected alveolar macrophages in our patient; however, our case does raise the possibility, which other reports have suggested,[2,7] that pulmonary involvement may occur very early in the course of HIV-1 infection.

Our patient's impaired diffusing capacity and mild hypoxemia returned to normal 2 weeks after hospital discharge, suggesting resolution of the alveolitis. He remains well 1 year after seroconversion.

This case emphasizes the importance of serial antibody testing in patients with suspected primary HIV-1 infection, since the time to detection of seroconversion may vary with different immunoassays. It also suggests that lymphocytic alveolitis may be a manifestation of acute HIV-1 infection and that primary involvement of the lung may occur very early following onset of infection.

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