Lymphocytic Bronchiolitis Associated with HIV Infection*

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Patients with the acquired immune deficiency syndrome (AIDS) frequently develop interstitial lung disease. This is due most commonly to opportunistic infections, but malignancy and lymphocytic interstitial pneumonitis have also been associated with the syndrome. In contrast, there has been little reported about airways disease in patients with HIV infection. We describe a patient with AIDS-related complex who presented with symptoms and radiographic evidence of micronodular interstitial lung disease. Transbronchial biopsy revealed a lymphocytic bronchiolitis but no evidence of interstitial lung disease and a marked T-suppressor lymphocytosis was found on analysis of the bronchoalveolar lavage (BAL) specimen. Routine fungal, viral and bacterial cultures did not yield an etiologic agent. This case raises the possibility that lymphocytic bronchiolitis may represent another pulmonary manifestation of HIV infection.

Patients with the acquired immune deficiency syndrome (AIDS) frequently develop interstitial lung disease (ILD). This is due most commonly to opportunistic infections, but malignancy and lymphocytic interstitial pneumonitis (LIP) have also been associated with the syndrome. A recent report indicates that obstructive airways disease may also exist in some AIDS patients, but little is known of its pathogenesis. We describe a patient with AIDS-related complex (ARC) who had symptoms and radiographic evidence consistent with nodular ILD, but on transbronchial biopsy there was evidence only of a lymphocytic bronchiolitis. Bronchoalveolar lavage (BAL) showed a marked T-suppressor lymphocytosis. Fungal, viral and bacterial culture results were negative. This case raises the possibility of a relationship between HIV infection and bronchiolitis and suggests that lymphocytosis in the BAL fluid in such patients may reflect bronchiolar inflammation.

**CASE REPORT**

A 23-year-old man with severe hemophilia (factor VIII, level <1 percent) was well until ten months prior to admission when he developed cutaneous herpes-zoster infection and oral candidiasis. HIV infection was confirmed by ELISA test and Western blot assay. A white blood cell count showed 3,500 cells/cu mm with a total lymphocyte count of 1,365 cells/cu mm. A T-helper/T-suppressor ratio was reduced at 0.1 (normal >1.0). He had been in a monogamous, heterosexual relationship, denied intravenous drug use, and had no unusual occupational exposure. He treated himself as needed with factor VIII concentrates (average 65,000 units per year).

Six months prior to admission, he developed malaise and generalized adenopathy, but denied fevers, chills or sweats. He had no previous pulmonary problems or allergies, and had never smoked cigarettes. Posteroanterior and lateral chest roentgenogram findings were normal. Three months prior to admission he noted exertional dyspnea, but denied cough, sputum production, hemoptysis, or wheezing. One month prior to admission he noted a nonproductive cough and increasing dyspnea. Repeat chest roentgenograms revealed subtle but diffuse, bilateral micro-nodular (2-5 mm in diameter) infiltrates without hilar adenopathy or evidence of fibrosis. Auscultation of the chest was normal. Bronchoscopy with transbronchial biopsy (eight specimens, left lower lobe) and BAL (lungula and a right middle lobe subsegment) using 120 ml of normal saline solution was performed which produced 1.89 x 10⁶ cells from the left lung, and 1.65 x 10⁶ cells from the right lung. The cell differentials from BAL of the left and right lungs were similar: alveolar macrophages (AlvM)—32.4 percent; lymphocytes (Ly)—78.6 percent; neutrophils (Pmn)—0.4 percent. Normal values for BAL analysis in our laboratory derived from 45 non-smoking normal volunteers (means ± SD) are: total cell number—8.0 ± 1.2 x 10⁶; AlvM—95.3 ± 2.3 percent; Ly—3.7 ± 0.35 percent; and Pmn—0.7 ± 0.1 percent. Helper/suppressor ratio of lymphocytes from BAL was 0.02 (normal >1.0). Stains for Pneumocystis and acid-fast bacteria were negative from both the biopsy and BAL specimens and no inclusion bodies were seen. The alveolar architecture was entirely normal, but there was an intense peribronchiolar infiltration of well differentiated lymphocytes with occasional plasma cells involving the terminal and respiratory bronchioles (Fig 1). Cultures of the bronchial washings and the lung tissue were negative for bacterial, fungal, or viral pathogens (including routine bacterial pathogens, acid-fast bacilli, cytomegalovirus, herpes simplex, adenovirus, enteroviruses and respiratory syncytial virus). There was no diagnostic rise in viral or Mycoplasma pneumoniae titers and cold agglutinins were not detected.

Pulmonary function test (PFT) results showed mild restrictive disease (total lung capacity [TLC]: 66 percent predicted; vital capacity: [VC] 76 percent predicted; functional residual capacity: 65

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**Figure 1.** Transbronchial biopsy specimen (hematoxylin and eosin, original magnification, × 160) showing lymphocyte and plasma cell infiltration of a terminal bronchiole (lumen, L) with normal adjacent alveoli.
percent predicted; residual volume: 35 percent predicted; and mild obstructive disease (FEV1/FVC ratio: 77 percent, predicted >85 percent) with a larger component of small airways disease manifest by reduction in the maximal mid-expiratory flow rate (51 percent predicted) and flow-volume loop evidence of diminished flow at low lung volumes without reversibility following bronchodilator administration. Carbon monoxide diffusion capacity (Dco) was 50 percent of predicted.

One month later he felt less dyspneic and had less cough. Repeat pulmonary function test results showed a slight increase in the Vc (85 percent predicted) and TLC (74 percent predicted), but Dco and flow rates remained unchanged. After three, six, and 12 months, PFT results showed identical obstructive changes and the patient reported stable but persistent dyspnea and cough. Repeat chest roentgenograms over this time have shown no change. The patient has been followed in an expectant manner without subsequent clinical deterioration or improvement after more than 18 months.

**DISCUSSION**

Interstitial lung disease from opportunistic infections, unusual malignancies, and LIP has been well documented in patients with AIDS. A recent report of unexplained airways obstruction in 50 percent of patients with AIDS raises the possibility that inflammatory airway disease may also be related to HIV infection. However, histologic evidence of airways disease independent of an infection or malignancy has been difficult to demonstrate in these patients since lung biopsies are usually performed only when there is clinical evidence for these processes. The current case raises the possibility that bronchiolitis may be causally related to HIV infection by the pathologic finding of peribronchiolar lymphocytic infiltrates in the absence of alveolar interstitial disease in a patient with ARC and no evidence of opportunistic pulmonary infection or malignancy.

"Usual" adult bronchiolitis is an uncommon disease. The chest roentgenogram, pulmonary function tests, and physical examination are consistent with the diagnosis of bronchiolitis in our patient. There was no evidence or historic data to implicate any known etiologic factor for bronchiolitis (eg, toxic vapor exposure, collagen vascular disease). While we cannot exclude etiology from other viruses either unassayed or unable to be cultured by current, standard techniques, the pathology and the lymphocytosis on BAL are unusual for "typical" adult bronchiolitis.

Lymphocytic interstitial pneumonia has recently been reported in several patients with AIDS or ARC and BAL has revealed lymphocyte predominance (35 and 38 percent of the total cell count) with decreased helper-suppressor ratio. It is a morphologic diagnosis seen in a number of immunologic disorders. It is possible that our patient has an early or less severe case of LIP and the characteristic alveolar interstitial infiltration with lymphocytes was missed by transbronchial biopsy. While we cannot exclude this possibility, over 200 normal alveoli were examined on the eight transbronchial biopsy specimens. Failure to demonstrate alveolar interstitial infiltrates on these specimens and lack of typical chest roentgenogram findings for LIP make this diagnosis less likely and the micronodular interstitial pattern on the chest roentgenogram is most consistent with the diagnosis of bronchiolitis. It is possible that HIV-related bronchiolar disease may represent one end of a spectrum of LIP in AIDS. In support of this concept, similar bronchial and bronchiolar disease and LIP with suppressor cell predominance on BAL have been reported as sequelae of bone marrow allograft.

While it is tempting to attribute the BAL lymphocytosis to the peribronchiolar lymphocytic infiltrates, no immunohistology was performed on the biopsy specimens to examine the phenotype of the tissue lymphocytes.

It is hoped that this case will serve to alert other clinicians to this possible pulmonary manifestation of HIV infection so that it may be further characterized. An important consideration is whether this patient's illness was an isolated occurrence or is representative of a larger population of HIV infected individuals (with or without AIDS) who may have obstructive lung disease. A recent report detailing "benign lymphocytic infiltration" of lung, kidneys, liver and salivary glands in five patients with ARC suggests that HIV infection can lead to a generalized lymphocytic infiltration process, the clinical importance of which depends upon the organ involved and the extent of the infiltration. The relationship between HIV infection and bronchiolitis and BAL suppressor-cell lymphocytosis remains to be further investigated. Local alteration in pulmonary anatomy (bronchiolitis) and immune balance (suppressor cell predominance) at the level of the acinus may prove to be important co-factors predisposing to the more life threatening opportunistic pulmonary infections in patients with AIDS.

**REFERENCES**