Interstitial lung disease and xerostomia as initial manifestations in a patient with human immunodeficiency virus infection

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A 56-year-old human immunodeficiency virus (HIV)-infected man presented with progressive interstitial lung disease (ILD) and lymphocyte infiltration of the salivary glands which mimicked autoimmune disease. Pneumonia, which was very likely caused by *Pneumocystis carinii*, developed after 3 courses of monthly methylprednisolone pulse therapy for ILD. Both enzyme immunoassay and Western blot analysis confirmed the HIV infection. After antibiotic treatment, the pneumonia gradually resolved. Autoimmune manifestations such as ILD and xerostomia may be initial presentations of HIV infection. Immunosuppressive drugs must be used cautiously in these patients. Screening for HIV is mandatory in the differential diagnosis of patients with ILD or xerostomia.

Key words: HIV, interstitial lung disease, lymphocytosis, xerostomia

There are protean manifestations of human immuno-deficiency virus (HIV) infection involving various organ systems. Rheumatologic manifestations of HIV infection include arthritis, myositis, vasculitis and the sicca complex-like syndrome. Previous reports found that among HIV-infected patients, 1.7% had Reiter's syndrome, 1.7% had psoriatic arthritis, and 11.1% had various forms of oligoarticular/monoarticular or polyarticular arthritis [1-4]. We describe an HIV-infected patient with the initial presentation of interstitial lung disease (ILD) and lymphocytic infiltration in the minor salivary glands who developed *Pneumocystis carinii* pneumonia (PCP) after 3 courses of monthly methylprednisolone pulse therapy.

Case Report

A 56-year-old homosexual man presented with body weight loss of over 10% and progressive air hunger without fever over a 2-month period. He had dry mouth but no eye dryness, vomiting or diarrhea. The parotid glands were not enlarged. Bulging out of the nasopharynx was noted in an otolaryngologic check-up, and evidence of chronic inflammation was found on histologic examination of nasopharynx biopsy. Hemoglobin was 11.3 g/dL, white cell count was 6000/µL with 44% neutrophils, 40% lymphocytes, 9% monocytes and 4.7% eosinophils. Platelet count was 178,000/µL. Results of liver function tests, renal function tests and urinalysis were normal. The C-reactive protein (CRP) was slightly elevated (0.5 mg/dL, normal less than 0.3 mg/dL). Tests for carcinoembryonic antigen, prostate specific antigen, α-fetoprotein, hepatitis B surface antigen and hepatitis C viral antigen were negative.

Chest radiograph showed interstitial infiltration in both lungs (Fig. 1) and computed tomography (CT) scan of the chest revealed diffuse ground glass change (Fig. 2). Bronchoscopic brushing cytology and transbronchial biopsy showed lymphocyte infiltration and fibrosis around the alveoli. A severe reduction in gas exchange capacity was demonstrated with a diffusion capacity of CO (37% of the predicted). Schirmer's test was negative but a salivary gland biopsy demonstrated more than 2 lymphocytic foci per 4 mm^2 of tissue. Sialoscintigraphy showed class III xerostomia (delayed glandular peak time: left, 59 min; right, 57 min; normal value <10 min). Antinuclear antibodies, rheumatoid factor, antibodies to scleroderma antigen 70 (Scl-70) and antibodies to Sjögren's syndrome antigen A (SS-A) [Ro] were negative. Immunoglobulin G (IgG) was 2740 mg/dL (normal, 751-1560 mg/dL),

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Fig. 1. Chest roentgenogram showing mild pulmonary interstitial infiltrations in the central zones of bilateral lungs.

IgA 354 mg/dL (normal, 82-453 mg/dL) and IgM 611 mg/dL (normal, 46-304 mg/dL). Because the ILD was suspected to have originated from autoimmune processes, monthly methylprednisolone (1000 mg once daily for 3 days) pulse therapy and daily azathioprine 50 mg were prescribed.

Dyspnea improved slightly during the first 2 courses of pulse therapy. However, on the 17th day after the third course of methylprednisolone pulse therapy, he developed fever, chills and dyspnea. Arterial blood

Fig. 3. Chest roentgenogram showing pulmonary infiltration over both lungs, which was more severe on the right side as shown by the presence of air bronchogram sign.

gas revealed moderate hypoxemia (pH 7.595, partial pressure of O_2 50.9 mmHg, partial pressure of CO_2 23.0 mm Hg, HCO_3^- 21.8 mmol/L, with fraction of inspired O_2 40%). CRP was 15.7 mg/dL. Chest radiograph showed pulmonary infiltration over bilateral lungs, which was more severe on the right side (Fig. 3). Chest CT scan revealed pneumonic processes with multiple abscess formation in the right middle and lower lobes, and alveolitis in the left lung (Fig. 4). Fever and dyspnea persisted despite intravenous cefazolin plus gentamicin administration for 3 days followed by another 3 days of cefuroxime plus gentamicin treatment. Gram-positive cocci were found in sputum. In view of
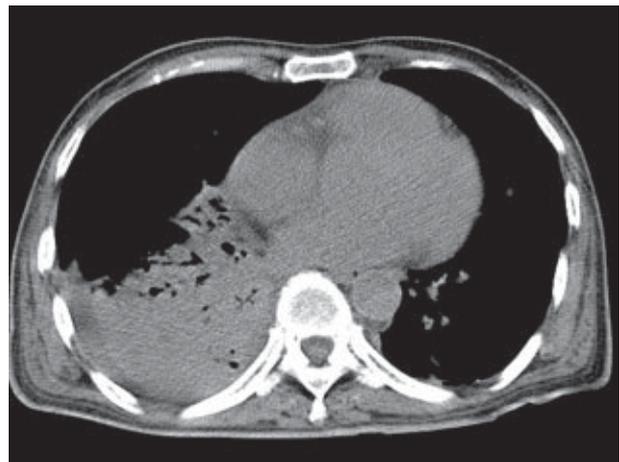

Fig. 2. Chest computed tomography scan showing diffuse ground glass opacities in both lungs and bronchial wall thickening with bronchial dilatation at the right lower lobe.

Fig. 4. Chest computed tomography scan showing consolidation of pulmonary parenchyma with gas shadows in the right middle lobe and right lower lobe.

the poor treatment effect, persistent hypoxemia and bilateral lung infiltration, staphylococcal, mycoplasma or PCP were suspected. Teicoplanin, ciprofloxacin and sulfamethoxazole-trimethoprim were given simultaneously. The ensuing laboratory investigations showed hemoglobin 9.5g/dL, white blood cell count 6100/μL (82% neutrophils, 9% lymphocytes, 10% monocytes), and platelet count 291,000/μL. Lymphocyte subpopulation analysis showed CD4 cells 4% and CD8 cells 85%. Both enzyme immunoassay and Western blot for HIV were positive. HIV viral loading test showed a viral copy number of 653,000 copies/mL. No pathogens were cultured from sputum and pleural effusion. Acid fast stain of the sputum smear and polymerase chain reaction for *Mycobacteria tuberculosis* from pleural effusion were negative. Serum IgG anti-cytomegalovirus antibody was positive but IgM anti-cytomegalovirus antibody was negative. Veneral disease research laboratory test, *Treponema pallidum* hemagglutination and serum cryptoccocal antigen were negative. Fever subsided and pneumonia resolved gradually after antibiotic therapy. Highly-active antiretroviral therapy was then started. Three months later, HIV viral load was undetectable and CD4 count was 248/μL.

Discussion

Diffuse infiltrative lymphocytosis syndrome (DILS) is characterized primarily by parotid gland enlargement, peripheral CD8 lymphocytosis, sicca syndrome and pulmonary involvement in HIV-infected subjects [5]. The prevalence of DILS is 3% in HIV-positive outpatients [6]. These patients have certain features that are unusual for the classic Sjögren's syndrome. They are predominantly men and none have significant levels of autoantibodies. Salivary gland biopsy specimens show diffuse lymphocytic infiltration of the glandular parenchyma without epithelial lesions. On the contrary, in classic Sjögren's syndrome, marked epithelial lesions are usually present [6,7].

Our patient was a homosexual male with progressive ILD and lymphocyte infiltration in salivary glands, which mimicked autoimmune disease. No auto-antibodies were detected. He had dry mouth but no obvious eye dryness or parotid gland enlargement. In this clinical context, others etiologies of Sjögren's-like syndrome should be considered. Malignant lymphoma, hepatitis C virus infection, and HIV infection have each been reported to be associated with Sjögren's syndrome [4,8,9].

Initially, our patient was thought to have connective tissue disease and progressive ILD. Due to progressive air hunger with severe reduction in gas exchange capacity, and the findings of chronic inflammation and fibrosis on transbronchial biopsy, monthly pulse glucocorticoid therapy was scheduled to ameliorate the pulmonary destruction [10].

Consolidation and abscesses in the lower and middle lobes of the right lung and alveolitis in the left lung developed, but sputum cultures did not yield any pathogens. He did not undergo bronchoscopy examination due to dyspnea with moderate hypoxemia. In view of the manifestations on CT scan and plain chest films, as well as the clinical features, PCP was considered to be the main cause of pulmonary inflammation. Patients with malignancies, immuno-deficiency, systemic glucocorticoid therapy with or without immunosuppressive drug treatment and connective tissue diseases are at risk of developing PCP [11-13]. The risk factors for PCP in our patient were systemic glucocorticoid therapy and HIV infection.

Pulmonary disorders, particularly respiratory infections, are an important cause of morbidity and mortality in HIV-infected individuals [14]. PCP remains the most common cause of life-threatening pulmonary infection in HIV-positive patients [15]. The classic radiographic presentation of PCP is a bilateral perihilar or diffuse symmetric interstitial pattern, which may be finely granular, reticular or ground glass in appearance [16,17]. The classic high-resolution CT finding for PCP is extensive ground glass attenuation, which corresponds to the presence of intra-alveolar exudates, consisting of fluid, organisms and debris [15].

In summary, ILD and xerostomia may be the first manifestations of HIV infection. Clinicians need to consider the possibility of concomitant HIV infection in patients from high-risk groups. Immunosuppressive drugs must be used cautiously in patients with auto-immune manifestations but without sufficient evidence to support the diagnosis. These patients may turn out to be HIV-infected individuals.

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