Lymphoid Interstitial Pneumonia Resolved Through Antiretroviral Therapy in an Adult Infected by Human Immunodeficiency Virus

R. García Luján, J.M. Echave-Sustaeta, C. García Quero, V. Pérez González, V. Villena Garrido, and A. López Encuentra

Servicio de Neumología, Hospital Universitario 12 de Octubre, Madrid, Spain.

Lymphoid interstitial pneumonia (LIP) is a rare entity characterized by the infiltration of interstitial tissues and alveolar spaces by lymphocytes, plasma cells, and other lymphoreticular structures. The etiology of LIP is unknown, although associations with autoimmune and infectious factors have been described. The incidence of LIP has risen in recent years, mainly in children with acquired immunodeficiency syndrome (AIDS), while remaining less common in the adult population. No agreement has been reached regarding the diagnostic tests necessary for a firm diagnosis although suspicion is usually based on clinical and radiographic findings, with confirmation provided by examination of histological samples. The most common treatment is corticosteroids, either alone or in combination with other immunosuppressant agents although no evidence from controlled trials is available and cases have been reported in which LIP resolved in AIDS patients with antiretroviral therapy alone. We report the case of a human immunodeficiency virus-infected adult who was diagnosed with LIP by open lung biopsy and who responded to antiretroviral drugs with no need for associated corticosteroid therapy.

Key words: Lymphoid interstitial pneumonia. HIV. Antiretroviral drugs.

Introduction

Lymphoid interstitial pneumonia (LIP) is a rare disease characterized histologically by an infiltration of the interstitial and alveolar spaces by lymphocytes, plasma cells, and other lymphoreticular structures. The etiology of LIP is unclear although associations with autoimmune and infectious factors have been described. The incidence of this disease has increased in recent years mainly among children with acquired immunodeficiency syndrome (AIDS), while remaining rare in the adult population. No agreement has been reached regarding the diagnostic tests necessary for a definitive diagnosis although suspicion is usually based on clinical and radiographic findings, and diagnosis should be confirmed by histology. Corticosteroids, alone or in combination with other agents, have been suggested as a treatment though no evidence from controlled trials is available and cases have been reported in which LIP resolved in AIDS patients with antiretroviral therapy alone.

We report the case of a human immunodeficiency virus (HIV)-infected adult who was diagnosed with LIP at our hospital by open lung biopsy and who responded to antiretroviral drugs with no need for associated corticosteroid therapy.

Correspondence: Dr. R. García Luján.
C/ Santiago de Compostela, 38, 6.º B. 28034 Madrid, España.
E-mail address: rglujan@hotmail.com

Manuscript received February 18, 2004. Accepted for publication March 9, 2004.
Case Description

The patient was a 45-year old man whose otherwise unremarkable history included a childhood episode of hemoptysis of unknown cause. In November of 1999 the patient developed asthenia and decreased appetite. Months later he consulted his primary care physician, who prescribed antibiotics. The patient did not respond to treatment and later developed progressive dyspnea with minimal exertion. A radiograph revealed left apical thickening with evident calcifications in the upper lobe and a bilateral alveolar interstitial infiltrate. Upon suspicion of pulmonary tuberculosis, tuberculous treatment was initiated. The patient did not respond to the treatment and it was suspended 4 weeks later because cultures were negative.

The patient was referred to our hospital in May of 2000 after progression of the infiltrate was detected in a new x-ray (Figure 1), and admission for testing was arranged. No anomalies or signs of diseased lymph nodes were noted upon physical examination. Dry crackles were heard in the lower third on both sides of the chest. The hemogram showed a white cell count of 3520 cells/µL (neutrophils: 45%; lymphocytes: 37%; monocytes: 11.8%) with an erythrocyte sedimentation rate of 95 mm/h. Biochemical tests demonstrated only an increase of the transaminases (aspartate aminotransferase: 53 IU/L; gamma-glutamyl transpeptidase: 46 IU/L); coagulation was normal and basal arterial blood gas analysis upon admittance revealed a pH of 7.39, PaO$_2$ of 62 mm Hg, and PaCO$_2$ of 36 mm Hg. HIV serology was positive (CD4: 281 cells/µL; viral load: 26 788 copies), and a Mantoux test was negative. Consultation of the patient revealed that the most likely route of contagion was sexual as he denied addiction to intravenous drugs. Lung function tests showed slightly restricted ventilatory impairment—forced vital capacity (FVC) of 3120 mL (74%), forced expiratory volume in 1 second (FEV$_1$) of 2560 mL (74%), and an FEV$_1$/FVC ratio of 82% (106%). All other serology tests (herpes simplex, syphilis, Epstein-Barr virus) were negative. A high resolution computed tomography scan of the chest showed an interstitial pattern along with apical lesions and calcified nodular images in the lower and middle fields indicative of prior disease.

Based on these findings it was decided to perform a bronchoscopy procedure with bronchoalveolar lavage. All the microbiological analyses (mycobacteria, virus, fungi, and *Pneumocystis carinii*) were negative and a predominance of CD8 lymphocytes was noted. A second bronchoscopy was performed some days later with transbronchial biopsy through segment 9 of the right lower lobe; pathological findings were consistent with atypical lymphoid proliferation. As no specific diagnosis had yet been established, it was decided to perform a lung biopsy through a left submammary minithoracotomy to remove samples of the lingula. The pathologist reported a polyclonal lymphoid proliferation consistent with LIP.

Because HIV-associated LIP was diagnosed, and the patient had remained clinically stable, it was decided to begin antiretroviral treatment. The patient was discharged and scheduled to come to our outpatient clinic after 2 months for clinical and radiographic follow up to assess the need for complementary corticosteroid therapy. Given the radiographic findings indicating prior pulmonary tuberculosis, secondary chemoprophylaxis with isoniazid was also started.

At the first outpatient revision, symptoms and basal arterial blood gases had improved (pH of 7.39; PaO$_2$, 76 mm Hg; and PaCO$_2$, 35 mm Hg). Lung function had also improved—FVC, 3680 mL (91%) and FEV$_1$, 2860 mL (86%). The CD4 lymphocyte count had increased to 425 cells/µL. Both the plain x-ray (Figure 2) and the high-resolution computed tomography scan showed significant improvement of the interstitial infiltrate in the middle and lower fields, and only the areas of pleural thickening and the prior calcifications persisted. These findings indicated that the patient was responding well to the antiretroviral treatment, and it was therefore decided not to prescribe complementary corticosteroids.

The antiretroviral treatment was interrupted in March of 2001 owing to intolerance. At this time the viral load was undetectable and the CD4 lymphocyte count was 675 cells/µL. The patient has continued periodic follow up in our clinic and has remained asymptomatic. Arterial blood gases and radiographs have indicated the patient is stable.
GARCÍA LUJÁN R, ET AL. LYMPHOID INTERSTITIAL PNEUMONIA RESOLVED THROUGH ANTIRETROVIRAL THERAPY IN AN ADULT INFECTED BY HUMAN IMMUNODEFICIENCY VIRUS

Discussion

LIP is a disease characterized histologically by a diffuse interstitial infiltrate arising from intense lymphocytic proliferation. The disease was first described by Carrington and Liebow in 1966. In children LIP is often associated with HIV infection, accounting for 40% of lung diseases in children with AIDS. In adults it is associated with autoimmune diseases such as Sjögren syndrome or primary biliary cirrhosis and accounts for merely 1% to 2% of lung diseases in adults with AIDS. A clear correlation has not yet been established between the development of this disease and the CD4 count.

It has been suggested that the cause of LIP is Epstein-Barr virus-related as DNA samples of this virus have been obtained in fragments of lung tissues taken from children with LIP. There are also LIP cases, in children as well as in adults, in whom the serology was Epstein-Barr positive. Moreover, there is general agreement that HIV itself plays a fundamental etiologic role because HIV RNA copies have been obtained in some lung biopsy samples, and HIV-specific immunoglobulin G is frequently present in the bronchoalveolar lavage fluid.

Clinical signs and symptoms are nonspecific and usually consist of dry cough, dyspnea on exertion, and fever. Fewer than 5% of the cases are asymptomatic at the time of diagnosis. Arterial blood gas analysis usually reveals hypoxemia with elevated alveolar-arterial oxygen difference, and spirometry normally shows a restrictive pattern with a decrease in lung volumes—decreased carbon monoxide diffusing capacity being the most sensitive marker. Although chest radiographs and computed tomography scans can show a variety of images, they generally reveal a reticulonodular interstitial pattern predominantly in the middle and lower lung fields with patchy areas of consolidation while the presence of lymph node involvement is fairly uncommon.

Bronchoalveolar lavage usually demonstrates lymphocytosis with prevalence of CD8 cells. For a firm diagnosis, the results of histology should be consistent. The samples may be obtained by bronchoscopic techniques although in general a surgical specimen is required either by open lung or thoracoscopic biopsy. The pathological findings consist of an infiltration of the alveolar septa by lymphocytes, plasma cells, and immunoblasts.

Little is known about the prognosis of LIP, whose clinical course ranges from spontaneous resolution to death related to respiratory failure due to pulmonary fibrosis.

There is no agreement on the treatment for LIP although treatment with corticosteroids at a dosage of 1 mg/kg/d is usually suggested, especially in severe and/or progressive forms. There is no evidence that antiretroviral treatment alone leads to improvement of the condition and, although some cases have been reported, in general such treatment is used in combination with corticosteroid treatment. However, the immunocompromised state of this subgroup of patients should be taken into account.

Given the immunological situation of our patient at the time of diagnosis along with the fact that he had remained clinically stable, we decided to start the patient on antiretroviral treatment and then at 2 months assess initial progress in order to decide if additional corticosteroid therapy would be necessary. Results of follow up revealed clear clinical, gasometric, and radiographic improvement of the LIP, which we attributed to the antiretroviral treatment and immunological improvement.

REFERENCES