

CASE REPORT

Lymphocytic bronchitis/bronchiolitis in a patient with primary biliary cirrhosis

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Lymphocytic bronchitis/bronchiolitis in a patient with primary biliary cirrhosis. G. Chatté, N. Streichenberger, O. Boillot, D. Gille, R. Loire, J-F. Cordier. ©ERS Journals Ltd 1995.

ABSTRACT: A 39 year old woman with severe primary biliary cirrhosis progressively developed exercise dyspnoea due to airflow obstruction. Sjögren's syndrome was not present. Bronchial and pulmonary biopsies demonstrated constrictive lymphocytic bronchitis/bronchiolitis, possibly a component of a generalized autoimmune process in this patient.

Eur Respir J., 1995, 8, 176–179.

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Keywords: Autoimmune diseases, biliary liver cirrhosis, bronchiolitis, bronchiolitis obliterans

Received: April 21 1994, Accepted after revision July 31 1994

Supported by grant HCL-PNRC 005 from Ministère de la Santé, France.

Primary biliary cirrhosis (PBC) is a chronic, progressive, cholestatic liver disease characterized by the inflammatory destruction of intrahepatic bile ducts, eventually leading to cirrhosis and liver failure. PBC is an autoimmune disorder, and patients have autoantibodies to mitochondria directed against components of the 2-oxo-acid dehydrogenase complex [1, 2]. PBC may be associated with other autoimmune disorders, such as Sjögren's syndrome [1]. Pulmonary manifestations have occasionally been reported in PBC, and include mild airways obstruction [3, 4], pulmonary haemorrhage [5], decreased carbon monoxide diffusing capacity, which may or may not be associated with clinical evidence of interstitial disease [3, 6], multiple lung granulomas [7], and subclinical lymphocytic alveolitis at bronchoalveolar lavage [8].

Lymphocytic bronchitis/bronchiolitis is a nonspecific type of airway disease, characterized by infiltration of the large and small airways by lymphocytes, which may organize into germinal centres (follicular bronchitis/bronchiolitis). This type of airway inflammation may occur in various conditions, such as infection, connective tissue disorders, and lung allografts, where it is suspected to represent a form of chronic rejection [9, 10].

We report a case of lymphocytic bronchitis/bronchiolitis developing in a patient with PBC, suggesting striking similarities between the pulmonary and hepatic disorders.

Case report

A 39 year old woman was referred to our hospital in May 1993 for respiratory evaluation before a decision

for liver transplantation. During the previous 3 yrs, she had complained of pruritus, fatigue, jaundice, nausea, and exercise dyspnoea. She had an 8 pack-year smoking history. There was no evidence of professional respiratory risk and she had never had asthma. In January 1993, hepatomegaly and chronic cholestasis led to a liver biopsy, which showed fibrosis bridging the portal triads, with follicular lymphomonocytic infiltration surrounding the bile ducts, consistent with stage 3 PBC. Pulmonary function testing demonstrated mild airways obstruction (table 1).

The patient presented in May 1993 with severe dyspnoea, productive cough, jaundice, and a 20 kg weight loss over the previous three months (present weight 40 kg). At physical examination, hepatomegaly, digital clubbing, inspiratory squeaks and expiratory rales were present. There was no clinical evidence of sicca syndrome, and a Schirmer test was negative. The patient was taking ursodeoxycholic acid every day, and had never received D-penicillamine. A chest X-ray showed moderate hyperinflation and discrete bilateral micronodular shadowing. A computed tomographic (CT) scan confirmed parenchymal distension, and revealed discrete subpleural nodules and widening of the bronchial walls.

Lung function tests and flow volume curves showed distal expiratory flow limitation, with no reduction of the transfer coefficient (table 1). Arterial blood gas measurements demonstrated hypoxaemia at rest and during exercise, with no venous admixture. A bronchoalveolar lavage (BAL) cell count showed 790 leucocytes- μl^{-1} with 73% polymorphonuclears, 8% lymphocytes, and 19% alveolar macrophages.

Table 1. – Pulmonary function tests

	January 1993	May 1993
FEV ₁ l	1.43	0.72
% pred	64	32
VC l	2.11	1.25
% pred	81	47
FEV ₁ /VC %	68	58
V ₅₀ l·s ⁻¹	1.28	0.50
% pred	34	13
V ₂₅ l·s ⁻¹	0.32	0.20
% pred	19	12
TLC l	NA	3.35
% pred		86
KCO mmol·min ⁻¹ ·kPa ⁻¹ ·l ⁻¹	NA	2.97
% pred		142

FEV₁: forced expiratory volume in one second; VC: vital capacity; V₅₀: expiratory flow at 50% VC; V₂₅: expiratory flow at 25% VC; TLC: total lung capacity; KCO: transfer coefficient of the lungs for carbon monoxide; % pred: % of predicted values; NA: not available.

Biological tests showed: total serum bilirubin 120 µmol·l⁻¹; alkaline phosphatases 820 IU·l⁻¹; serum proteins 86 g·l⁻¹; serum albumin 42 g·l⁻¹; serum immunoglobulin G (IgG) 23 g·l⁻¹; serum immunoglobulin M (IgM) 5.4 g·l⁻¹; alpha¹-antitrypsin 3.98 g·l⁻¹; white blood cells 9.4 g·l⁻¹ with 66% polymorphonuclears, 2% eosinophils, and 28% lymphocytes; circulating immune complexes 9.7 mg·l⁻¹ (normal value <3.5 mg·l⁻¹); rheumatoid factor 47 IU (normal value <30 IU); antinuclear antibodies 1/4096 (normal value <1/64); antimitochondrial antibodies 1,600 U (normal value <30U); anti-La (SSB), anti-Ro (SSA), anti-Sm, anti-RNP antibodies were not detectable. Bacterial, fungal, viral, and mycobacterial cultures of the BAL fluid were sterile. Serological tests for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, adenovirus and paramyxovirus were negative. Bronchial and lung biopsies provided a diagnosis of lymphocytic bronchitis/bronchiolitis. Methylprednisolone was started (1 mg·kg⁻¹ daily) with azathioprine (1.25 mg·kg⁻¹ daily), together with fenoterol (6×200 µg·day⁻¹). The patient improved transiently, with a better exercise capacity. However, she was readmitted 6 weeks later for worsening of her condition and cachexia, and was referred to the intensive care unit for acute respiratory failure. Blood and BAL cultures were positive for *Staphylococcus aureus*, and the patient died of septic shock. Permission for autopsy was not obtained.

Pathological findings

Bronchial biopsies obtained by fiberoptic bronchoscopy showed a submucosal diffuse lymphoplasmacytic infiltration with mild fibrosis. Lung biopsy, performed by video-assisted surgery, showed changes with an airway-centred distribution. Several aspects of bronchiolar disease were found. The most consistent and characteristic abnormality consisted of mixed lymphocytic and plasmacytic infiltrates involving the entire wall of most of the bronchioles ("cellular bronchiolitis"); the infiltrate

was diffuse (fig. 1) or nodular (fig. 2), but only occasionally follicular. In the less damaged bronchioles, the mononuclear infiltrate did not alter the calibre of the lumen; in the more severely affected ones, concentric submucosal fibrosis and scarring constricted the lumen of the airway, sometimes leading to bronchiolar destruction with fibrous occlusion of the airway. A few regions of bronchiolectasis with mucus stasis were found. Mononuclear cells were present within the bronchiolar epithelium. Some bronchiolar metaplasia was also present, and extended to the peribronchiolar alveolar septa. The alveolar interstitium was not significantly impaired, with only occasional lymphocytic infiltrates and little fibrosis. There was no vasculitis.

Immunohistochemical studies showed that the concentric submucosal mural infiltrate of the bronchioles was composed of equal proportions of T-lymphocytes (expressing the CD3, CD5 and CD7 cytodifferentiation antigens) and B-lymphocytes (expressing the CD20, and L26 cytodifferentiation antigens). About two thirds of the T-lymphocytes were CD8+ (cytotoxic/suppressor cells) and one third CD4+ (helper/inducer cells), and the two types were intermingled. Cells expressing CD57 cytodifferentiation antigen (natural killer/T-cells) were extremely rare. Few dendritic cells (expressing the cytodifferentiation antigen CD1) were present in peribronchiolar nodules. Within the bronchiolar epithelium, almost

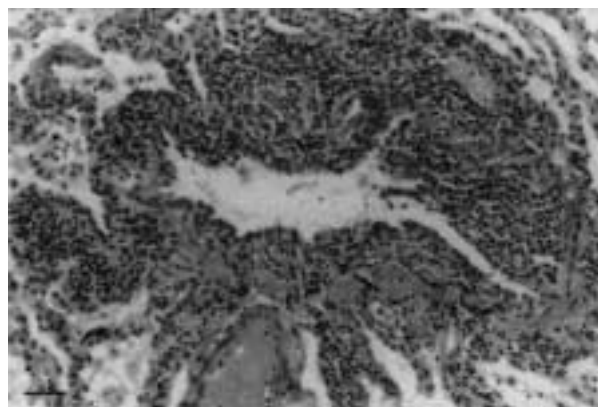


Fig. 1. – Diffuse mural lymphocytic bronchiolitis with submucosal fibrosis and bronchiolar metaplasia. (Scale bar = 50 µm).

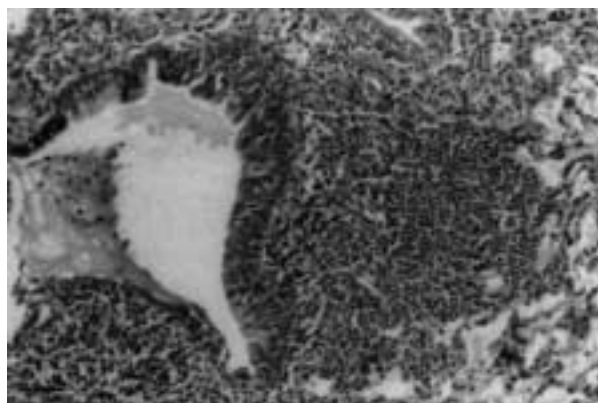


Fig. 2. – Nodular lymphocytic infiltrate in the wall of a bronchiole. (Scale bar = 50 µm).

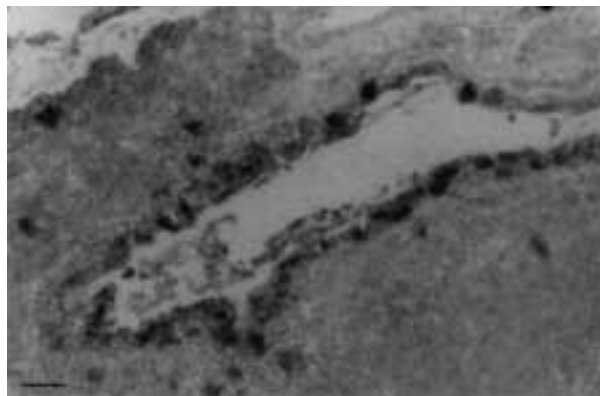


Fig. 3. – Numerous dendritic cells (expressing the CD1 cytodifferentiation antigen) are present throughout the bronchiolar epithelium. (Scale bar = 50 μ m).

all mononuclear inflammatory cells were T-lymphocytes, with a predominance of CD8+ cells. Numerous dendritic cells were present and distributed throughout the epithelium (fig. 3).

Discussion

Although our patient had an 8 pack-year smoking history, her rapidly progressive airflow obstruction and, especially, the pathological pulmonary changes cannot reasonably be related to the usual airway changes observed in smokers [11]. She had lymphocytic bronchitis/bronchiolitis, which resulted in severe airflow obstruction resembling that seen in the group of "constrictive" bronchiolitis, where the inflammation and eventual subsequent fibrosis are submucosal and peribronchiolar in distribution [12]. This type of airway disorder has been well-described in lung transplant patients, where it might represent an alloreactive injury consequent to allograft rejection, and is associated with the development of bronchiolitis obliterans [9]. Lymphocytic bronchitis/bronchiolitis has also been reported in patients with rheumatoid arthritis and/or Sjögren's syndrome [10, 13]. Although Sjögren's syndrome or decreased secretion is known to be present in a majority of patients with PBC [14, 15], this was not the case in our patient, in whom both clinical examination for sicca syndrome and a Schirmer test for decreased lachrymal secretion were negative, thus ruling out Sjögren's syndrome as the cause of the airway disease.

Airflow obstruction has occasionally been reported in patients with PBC. Mild airflow obstruction was present in four of a series of 67 patients with PBC, and sicca syndrome was present in all four [3]. Airflow obstruction with pathological evidence of lymphocytic bronchiolitis has also been reported in a patient with PBC and Sjögren's syndrome ([16], and Tong MJ, personal communication). The originality of the present case is that the airway disorder with airflow obstruction occurred in the absence of a detectable Sjögren's syndrome associated with the PBC.

The outcome of lymphocytic bronchitis/bronchiolitis

is not precisely known, with some patients improving on corticosteroids whilst others continue to deteriorate and eventually die of their pulmonary disease [10]. The prognosis of the airway disorder probably depends largely upon its cause and the clinical context of occurrence. In our patient, a transient clinical improvement was observed under corticosteroid treatment, with a decrease of exercise dyspnoea. However, her general condition, which was precarious, deteriorated rapidly and she died of septicæmia. We, thus, do not know if her bronchiolitis was reversible or not.

The resemblance of the histological changes to the liver in PBC and in hepatic graft *versus* host disease or rejection of a hepatic allograft has been described [1, 17], and involves a periductular lymphocytic infiltration leading to obliteration and destruction of the bile ducts. Lymphocytic bronchitis/bronchiolitis occurring in lung and allogeneic bone marrow transplant patients has also been interpreted as rejection and as a graft *versus* host reaction, respectively, [9, 18]. The occurrence in our patient of an immunological process resembling rejection or graft *versus* host reaction in both a pulmonary and hepatic setting is, thus, not surprising, and suggests a systemic autoimmune disorder simultaneously affecting both organs. It has been speculated that the pathogenic process of PBC could be due to the induction of aberrant class II human leucocyte antigens on bile duct epithelial cells, leading to injury by cytotoxic T-cells [2]. However, this hypothesis has not been confirmed by hepatic immunohistochemical studies, which indeed have found a general rather than a specific lymphoid immunologic process, involving intermingled CD4 and CD8-T-cells, and B-cells [19].

Pulmonary immunohistochemical analysis in our patient gave similar data, reinforcing the resemblance of the hepatic and pulmonary processes. In our patient, many dendritic cells were present within the bronchiolar epithelium, a finding also reported in post-lung-transplant bronchiolitis [20].

The present case report suggests that lymphocytic bronchitis/bronchiolitis may be part of a generalized autoimmune process in PBC, and not necessarily the mere consequence of Sjögren's syndrome.

Acknowledgements: The authors thank L.E. Adinolfi, for communicating the histological slides of liver biopsy.

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