Clin Rheumatol (2007) 26:1339–1343
DOI 10.1007/s10067-006-0351-x

CASE REPORT

Lymphocytic interstitial pneumonitis (LIP) in Sjögren's syndrome: a case report and a review of the literature

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Received: 2 April 2006 / Revised: 18 May 2006 / Accepted: 18 May 2006 / Published online: 5 August 2006

Abstract Sjõgren's disease is one of the most common rheumatological diseases and can present with a variety of extra-glandular manifestations. Lymphocytic Interstitial Pneumonitis (LIP) is the most common lung pathology in these patients. It is important to know and recognize this condition because it is potentially treatable. It is also frequently misdiagnosed and treated as infectious pneumonia multiple times before the correct diagnosis is made. It is a benign lymphoproliferative disorder characterized histologically by interstitial infiltration with polyclonal lymphocytes and plasma cells. High-resolution CT scan of the lungs shows extensive areas of ground-glass attenuation and interlobular septal thickening with scattered thin-walled cysts. An open-lung biopsy is the best method of diagnosing this condition, as less invasive techniques do not provide an adequate tissue specimen. LIP occurs in a wide variety of settings such as autoimmune disease, HIV disease, and as an adverse reaction to some medications; it is, therefore, considered to be a nonspecific response to many stimuli. The treatment usually consists of corticosteroids and other immunosuppressants, though there have been no controlled trials to date. Establishment of a registry may help better evaluate and treat this disease. We present the case of a patient who was diagnosed with LIP secondary to Sjögren's syndrome and also review the literature available.

Keywords Lymphocytic interstitial pneumonitis · Lymphoproliferative disorder · Sjögren's syndrome

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Introduction

Sjögren's syndrome is characterized by a clinical triad of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and arthritis. It is a common condition that affects 0.1% of the general population and 3% of older adults. It is classified as primary (without features of other connective tissue diseases) or secondary (in association with other autoimmune disorders, e.g., rheumatoid arthritis).

Sjögren's syndrome has numerous extra-glandular manifestations, including lung involvement. The most common pulmonary complication is lymphocytic interstitial pneumonia or LIP. This is followed, in decreasing frequency, by other abnormalities like follicular bronchitis, bronchiectasis, bronchiolitis, fibrosis, bronchiolitis obliterans organizing pneumonia, lymphoma, pulmonary hypertension, pleural effusion, and fibrosis [1].

LIP is a benign lymphoproliferative disorder characterized by diffuse proliferation of the pulmonary parenchymal interstitium by polyclonal lymphocytes and plasma cells [2].

It is important to recognize LIP in patients with Sjögren's syndrome because of its nonspecific clinical presentation that may be mistaken for infectious pneumonia. This results in a delay in correct treatment, which consists of corticosteroids with or without additional immunosuppressive medications.

We present such a case to highlight this fact.

A 28-year-old African-American female presented with dry cough, shortness of breath on exertion, fever, and night sweats for 4 months. She had been diagnosed twice recently for infectious pneumonia and treated with antibiotics without much relief of her symptoms. A review of systems was positive for dry mouth, grittiness in her eyes, and painless lymph node enlargement in the neck.

She had a history of mild childhood asthma controlled with albuterol inhaler. She had no known allergies or surgical history. She worked in a grocery store and was exposed to passive smoking at home. Her family history was otherwise noncontributory.

Her vital signs showed no fever, tachycardia (103/min), mild tachypnea (18/min) and a normal blood pressure. Her oxygen saturation at room air was 92%.

Her physical examination revealed enlarged lymph nodes bilaterally in the anterior cervical chain, axillary nodes, and inguinal nodes. They were about 1 cm in size, discrete, and freely mobile. She had no accessory muscle use, and her lung exam showed bibasilar rales up to the mid-thorax level. She had mild canthal congestion, and no parotid enlargement. The rest of the physical examination was unremarkable. Laboratory tests were as follows:

- Hb 11.4 g/dl, Hct 33.5, white cell count 4.6×10^3/cumm, platelets 218×10^3/cumm
- Differential count: 49 neutrophils, 39 lymphocytes, 8 monocytes, 2 eosinophils, and 2 basophils. A basic metabolic panel was normal.
- Liver function test showed mild elevation of aminotransferases: bilirubin 0.4, AST 56, ALT 46, total protein 8.1, alkaline phosphatase 63, and albumin 3.9
- ABG on room air showed significant hypoxia: pH 7.44, pO2 53 mm Hg, pCO_2 42 mmHg

A CAT scan of the chest confirmed extensive bilateral axillary lymphadenopathy, as well as supraclavicular and superior mediastinal lymphadenopathy (Fig. 1). No hilar lymphadenopathy was seen. The lungs showed ground-glass opacification of the posterior segments of both lower lobes with superimposed areas of basilar bronchiectasis as well as moderate alveolar consolidation, predominantly of the posterior segment of the right lower lobe. Thin-walled small cysts were seen in the right upper lobe associated with prominent focal bronchiectatic segments (Fig. 2).

Abdominal CAT scan showed bilateral inguinal lymphadenopathy.

The diagnoses initially entertained included lymphoma, fungal pneumonias, sarcoidosis, and the interstitial pneumonitides.

An axillary lymph node biopsy showed marked lymphoid hyperplasia and reactive changes but was negative for granulomas or atypical cells suggestive of lymphoma.

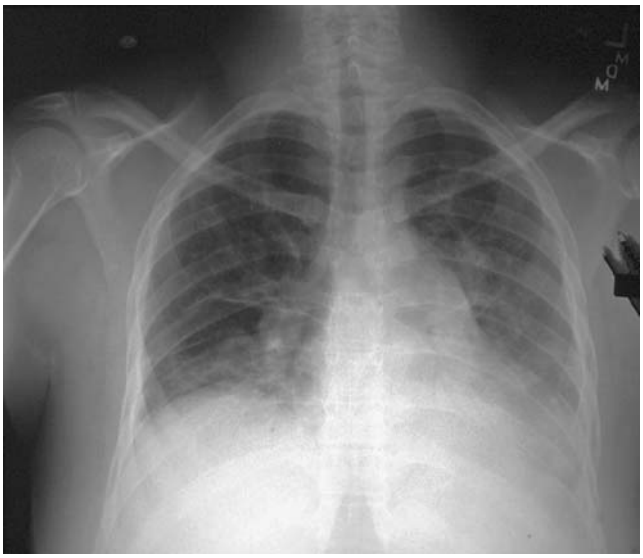

Fig. 1 A chest radiograph shows bilateral interstitial infiltrates, more prominent in the lower and mid-lung zones

Cultures of the node for viruses, fungi, bacteria, and acid-fast bacilli were negative.

Pulmonary function testing revealed a restrictive pattern with decreased diffusion capacity. A right-sided thoracoscopy was done with biopsies taken from all three lobes of the right lung and paraesophageal nodes. Microscopic analysis showed similar histology in all samples. Each showed varying degrees of a prominent interstitial expansion of a mixed lymphoplasmacytic infiltrate together with a follicular bronchiolitis, suggestive of lymphocytic interstitial pneumonia (Fig. 3). Further tests were performed to determine an underlying cause for these findings.

A methenamine silver stain for PCP was negative. HIV test was nonreactive.

ANA >1:640, speckled pattern

SSA (Ro) positive, SSB (La) positive

DsDNA antibodies were weakly positive.

ESR 65 mm/h

RA factor positive

U1RNP/snRNP IgG autoantibodies were positive.

A complete hepatitis panel was negative.

Serum protein electrophoresis showed hypergammaglobulinemia without a monoclonal protein.

Schirmer's test for dry eyes was positive.

Based on the above tests, the patient's final diagnosis was LIP secondary to primary Sjögren's syndrome. She was initially treated with intravenous methylprednisolone 80 mg every 8 h for 4 days followed by oral prednisone, which was tapered slowly over 9 months, and then maintained on azathioprine 75 mg orally daily and hydroxychloroquine 400 mg orally daily. Her lung function and radiologic picture showed considerable improvement in

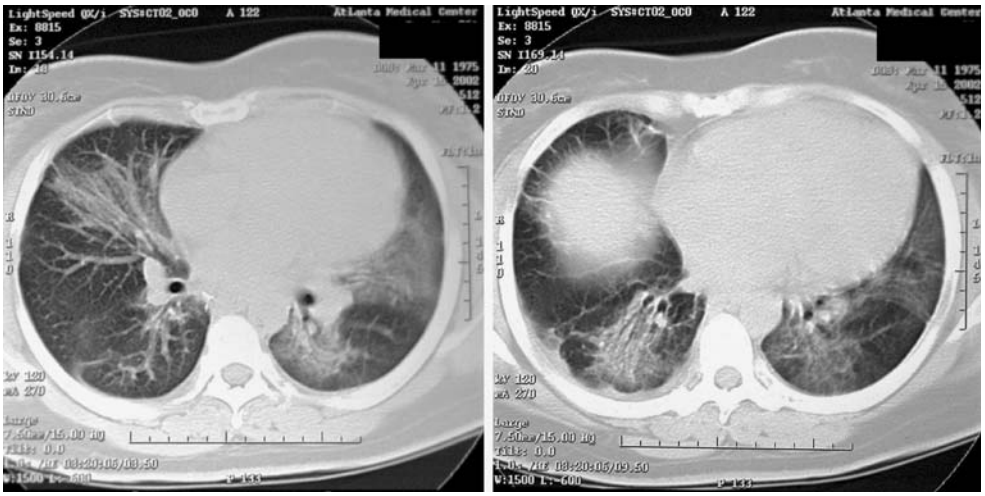

Fig. 2 CAT scan findings

6 months, and she has remained stable for more than a year of follow-up.

Clinical features of lymphocytic interstitial pneumonitis (LIP)

LIP has a female preponderance. The mean age at diagnosis is 52–56 years. Most HIV-negative adults with LIP are white [3, 4]. Respiratory symptoms are present in the majority of patients at the time of diagnosis and include progressive dyspnea and dry cough [4–6]. Systemic symptoms such as fever, night sweats, and weight loss are less common. The mean time from presentation to diagnosis can exceed 15 months [5].

Lung auscultation often reveals bibasilar crackles [4]. Clubbing is usually absent [3, 4].

Pulmonary function studies usually show a restrictive ventilatory defect with a decreased carbon monoxide diffusing capacity and variable levels of hypoxemia [3].

Approximately 80% of patients with LIP have serum dysproteinemias; most commonly, polyclonal hypergammaglobulimia [3, 4, 7]. The cause of this is unknown, however; it likely reflects chronic systemic autoimmune inflammation.

Radiologic features

The chest X-ray usually shows nonspecific bilateral reticular or reticulonodular opacities. However, the distinguishing clinical feature of these findings in LIP is their chronicity and lack of response to treatments that would usually resolve other pulmonary conditions such as antimicrobial therapy [8].

High-resolution CT scan is the imaging of choice, which shows a characteristic pattern of areas of ground-glass attenuation with scattered thin-walled cysts in about 50% of patients with LIP [9, 10]. Centrilobular nodules, patchy bronchovascular bundle thickening, and interlobular septal thickening are also very common and represent expansion of the interstitial tissue by lymphoplasmacytic cell infiltration [9]. Airspace disease, pleural effusions, and large nodules are rare.

Histopathology

Microscopically, LIP is characterized by diffuse interstitial infiltrates composed of a mixture of small lymphocytes, plasma cells and histiocytes, which expand and widen the interlobular and alveolar septae.

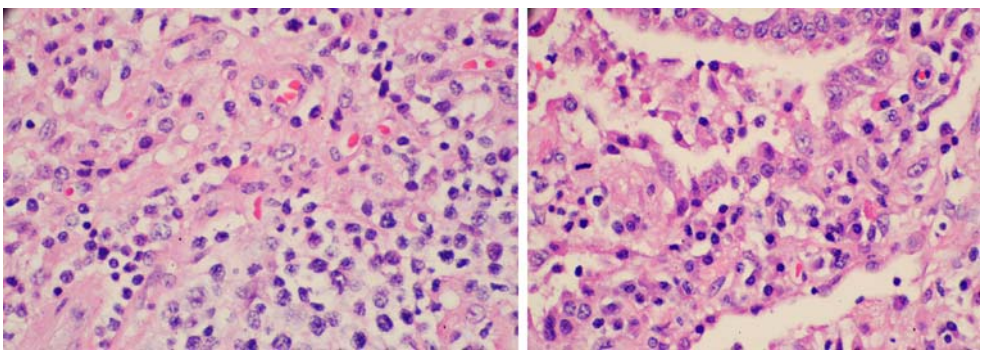

Fig. 3 Histopathologic findings, as described in the text

Interstitial fibrosis and honeycombing is reported in advanced cases [5, 11]. The interstitial lymphoid cells are mainly T cells, while B cells are located in peribronchial germinal centers [7]. Similar features are also seen in salivary glands of patients with Sjögren's syndrome.

The histopathologic differential diagnosis of LIP includes lymphomatoid granulomatosis, hypersensitivity pneumonitis, small lymphocytic lymphoma, and MALTomas.

LIP is differentiated from lymphomas by the polyclonal nature of its lymphocytes compared to the monoclonality seen in lymphomas. Due to its association with immunocompromised states, stains for *Pneumocystis carinii* must be carried out in all patients.

Treatment and prognosis

Treatment is based on anecdotal experience. Corticosteroids are the traditional primary therapy, but other immunosuppressive agents such as cyclophosphamide, chlorambucil [3], and azathioprine have been used [2] with variable results. Some patients improve without therapy, while others progress to advanced interstitial fibrosis despite immunosuppression. A recommended regimen [12] is to use prednisone, 1.0 mg/kg/day for 8 to 12 weeks or until stabilization. Then the dose is slowly tapered to 0.25 mg/kg/day and kept at that dose for another 6 to 12 weeks. Approximately 50 to 60% of patients have responded to corticosteroids with symptomatic or radiographic stabilization or improvement [4].

Discussion

The frequency of lung disease in Sjögren's syndrome ranges widely between 9 and 50%, based on the evaluation procedures employed [2, 13, 14]. Some earlier studies showed more severe lung disease in the secondary form, but later studies showed a high incidence of lung disease in primary Sjögren's syndrome as well [13].

LIP is often seen in association with systemic diseases, of which HIV infection and Sjögren's syndrome are the most common. One percent of Sjögren's patients develop LIP during their lifetime [3, 5]. Conversely, 25% of LIP cases are associated with Sjögren's syndrome.

LIP also occurs in other autoimmune diseases, including systemic lupus erythematosus [15], rheumatoid arthritis, autoimmune thyroiditis [4], myasthenia gravis [4], hemolytic [4] and pernicious anemia, auto erythrocyte sensitization syndrome, chronic active hepatitis, celiac sprue, primary biliary cirrhosis [3, 7], common variable immunodeficiency and as a late complication of allogeneic bone marrow transplant.

As LIP occurs in diverse settings such as infection and autoimmune diseases, it is thought to represent a nonspecific response to multiple stimuli [16]. After Liebow and Carrington first described it in 1966, they suggested many etiologic factors including viruses, either by a direct action or by disturbing immune surveillance mechanisms in the lung. Epstein–Barr virus has been found in the lungs of some but not all patients with LIP [17]. Antibodies to HTLV-1 have also been found in patients with LIP [16]. This supports the role of viruses in some instances of LIP.

Conclusion

Sjögren's syndrome is a common rheumatologic disorder characterized by the destruction of exocrine glands. Pulmonary manifestations are common during the evolution of this disease ranging from tracheobronchitis to interstitial lung disease, to malignant lymphoproliferative disorders. LIP is one of the complex polyclonal disorders, which is commonly associated with Sjögren's and is potentially treatable.

Clinicians need to be aware of this entity, and consider lung biopsy in patients presenting with pulmonary symptoms not responding to conventional treatment.

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