CHEST

Original Research

INTERSTITIAL LUNG DISEASE

Interstitial Lung Disease in Primary Sjögren Syndrome*

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Background: **Primary Sjögren syndrome (pSS) has been associated with various histologic patterns of interstitial lung disease (ILD).**

Methods: **We retrospectively identified 18 patients with pSS and suspected ILD who underwent lung biopsies (14 surgical biopsies and 9 bronchoscopic biopsies) at our institution during a 13-year period from 1992 through 2004. Histopathologic findings were analyzed and correlated with radiologic features and outcome.**

Results: **Median age was 62 years (range, 34 to 78 years), and 15 patients (83%) were women. Most patients presented with dyspnea and cough. Chest radiographs demonstrated bilateral infiltrates, and high-resolution CT revealed abnormalities of various types including ground-glass, consolidation, reticular, and nodular opacities. The major histopathologic patterns included nonspecific interstitial pneumonia (NSIP) [five patients], organizing pneumonia (OP) [four patients], usual interstitial pneumonia (UIP) [three patients], lymphocytic interstitial pneumonia (three patients), primary pulmonary lymphoma (two patients), and diffuse interstitial amyloidosis (one patient). In four patients (three with OP and one with amyloidosis), the diagnosis was established on transbronchial biopsy results. Treatment commonly included prednisone with or without another immunosuppressive agent. During the follow-up period (median, 38 months), most patients improved or remained stable except three patients with UIP, one patient with NSIP, and one patient with amyloidosis. Seven patients (39%) died, including three deaths from acute exacerbation of interstitial pneumonia.**

Conclusions: **A variety of histologic patterns can be seen in patients with pSS-associated ILD. Those with UIP tended to have progression of lung disease. Death from acute exacerbation of interstitial pneumonia may occur in patients with pSS-associated ILD.**

(CHEST 2006; 130:1489–1495)

Key words: interstitial lung disease; interstitial pneumonia; lung biopsy; pulmonary fibrosis; Sjögren syndrome

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; ILD = interstitial lung disease; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PASP = pulmonary artery systolic pressure; PFT = pulmonary function testing; pSS = primary Sjögren syndrome; UIP = usual interstitial pneumonia

Primary Sjögren syndrome (pSS) is a systemic inflammatory disorder that commonly affects exocrine glands.[1,2] Although sicca features are the central clinical manifestations of the disease, pSS can cause systemic extraglandular manifestations. The reported frequency of pulmonary involvement in pSS varies widely, ranging from 9 to 75% depending on the detection method employed, and consists of various forms of small airways and interstitial lung diseases (ILDs).[3–6]

Aside from a well-established association with lymphocytic interstitial pneumonia (LIP),[3–6] there is

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Funding was provided by the Mayo Foundation.

None of the authors have any conflicts of interest to disclose.

Manuscript received March 13, 2006; revision accepted May 8, 2006.

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DOI: 10.1378/chest.130.5.1489

relatively little information regarding other ILD patterns occurring in patients with pSS. We characterized histologic patterns of ILD associated with pSS by examining a consecutive series of these patients seen at our institution. We also correlated these histologic findings with clinicoradiologic presentations and outcomes.

Materials and Methods

Patient Selection

A computer-aided search was conducted to retrospectively identify all adults (≥ 18 years old) seen at our institution during the 13-year period from January 1, 1992, to December 31, 2004, with pSS and either pulmonary fibrosis, interstitial pneumonia, or suspected ILD. We identified 32 patients with pSS and ILD who had no identifiable cause for their lung disease other than the underlying connective tissue disease. Eighteen of these 32 patients had lung biopsies performed for histopathologic diagnosis of persistent bilateral lung infiltrates and formed the final study group.

Diagnostic Criteria

The American-European classification criteria[7] were used to make the diagnosis of pSS and included the following items: ocular symptoms of inadequate tear production, oral symptoms of decreased saliva production, ocular signs of corneal damage due to inadequate tearing, salivary gland histopathology demonstrating foci of lymphocytes, test results indicating impaired salivary gland function, and the presence of autoantibodies (anti-SS-A/Ro, anti-SS-B/La, or both). Definite diagnosis of pSS required the presence of four of the six items with histopathologic findings or autoantibodies being one of the four items. The diagnosis of ILD required the persistent presence of bilateral parenchymal lung infiltrates by chest radiography and/or CT. Patients with transient or focal infiltrates were excluded. We limited the analyses to patients with pSS by excluding those with underlying connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis/dermatomyositis, scleroderma, and mixed connective tissue disease. We also excluded patients with preexisting lymphoma, sarcoidosis, infection with HIV or hepatitis C virus, prior head and/or neck irradiation, recent use of drugs with anticholinergic properties, and graft-vs-host disease.

Clinical, Laboratory, and Radiologic Data

Clinical data and diagnostic results were extracted from the medical records and included demographic data, clinical presentation, physical findings, laboratory results, radiologic findings, and echocardiographic data. Presenting signs and symptoms were recorded from the first encounter at our institution that led to a diagnosis of pSS-associated ILD. Pulmonary function data included plethysmographically determined total lung capacity and residual volume, along with FVC, FEV_1, ratio of FEV_1 to FVC, and diffusing capacity for carbon monoxide (DLCO). Spirometry and measurements of lung volumes and DLCO were performed in our pulmonary function laboratory and were expressed as percentage of predicted normal values, using previously described techniques.[8] All expressed values are mean ± SD unless stated otherwise. Chest radiographs and CTs of the lungs were reviewed and interpreted without knowledge of biopsy results or clinical manifestations by a chest radiologist with a specific interest in ILD (R.M.L).

Surgical lung biopsy slides were retrieved and reviewed by a pulmonary pathologist (J.L.M.) without knowledge of clinical or radiologic information. The histopathologic diagnosis was made using terminology proposed in the American-European consensus statement on idiopathic interstitial pneumonias.[9] The Mayo Foundation Institutional Review Board approved this study. Patients who did not authorize the use of their medical records for research were excluded from this study.

Results

Clinical Features

The median age of our 18 patients at the time of lung biopsy was 62 years (range, 34 to 78 years), and 15 patients (83%) were women. Four patients (22%) had a smoking history and included one current smoker. Four of the 18 patients (22%) had both pSS and ILD diagnosed within 1 month of their initial presentation. The remaining 14 patients (78%) had pSS diagnosed prior to diagnosis of lung disease (median interval, 6.3 years; range, 1.2 to 9.8 years). Clinical features at initial presentation are summarized in Table 1. All patients had respiratory symptoms, most commonly exertional dyspnea. The duration of respiratory symptoms ranged from 3 to 12 months (median, 7 months) prior to lung biopsy.

Laboratory Findings

Laboratory results are summarized in Table 2 and included the presence of anti-nuclear antibody and anti-SS-A/Ro antibody in nearly all patients tested. Polyclonal hypergammaglobulinemia, an elevated erythrocyte sedimentation rate, and elevated rheumatoid factor titers were also evident in most patients. Anti-SS-B/La antibody was detected in one half of patients. Labial salivary gland biopsies were

Table 1—*Presenting Symptoms and Signs*

Variables	No. (%)
Symptoms	
Dyspnea	17 (94)
Cough	12 (67)
Chest pain	4 (22)
Wheeze	3 (17)
Fever	1 (6)
Sicca symptoms*	14 (78)
Physical findings	
Inspiratory crackles	12 (67)
Expiratory wheezes	3 (17)
Digital clubbing	1 (6)
Normal lung examination	5 (28)

*Sicca symptoms included dry eyes in 14 patients (78%) and dry mouth in 10 patients (56%).