Respiratory Manifestations in Primary Sjögren’s Syndrome*

A Clinical, Functional, and Histologic Study

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Thirty-six patients with primary Sjögren’s syndrome were evaluated for respiratory manifestations using clinical, roentgenologic, functional, and in five cases, histologic criteria. Twenty seven patients (75 percent) had evidence of respiratory involvement, usually occurring early in the course of the disease. Diffuse interstitial lung disease was most common (25 percent) followed by small airways disease (22 percent), desiccation of upper respiratory tract (17 percent) and large airways obstruction (8 percent). There was no patient with pleural effusion. Transbronchial lung biopsy of five patients studied revealed interstitial pathology ranging from dense lymphocytic infiltrates to interstitial fibrosis. Roentgenologic evaluation was often suggestive of interstitial lung disease but did not correlate with functional or histologic findings.

The natural history and frequency of respiratory involvement in primary Sjögren’s syndrome remain a subject of considerable controversy in spite of the growing literature on the subject. This is probably a result of differences in the populations and methods applied in the individual studies. The population of most studies is mixed, including patients with both primary and secondary Sjögren’s syndrome, while the methods used to study the respiratory system vary from mainly clinical to mainly functional. Finally, the number of patients with primary Sjögren’s syndrome in most studies is small, resulting in conflicting estimates of the respiratory functional abnormality.

Since involvement of the respiratory system in patients with secondary Sjögren’s syndrome can be a result of both Sjögren’s syndrome and the underlying rheumatic disease, we thought that a comprehensive study using a large number of patients with exclusively primary Sjögren’s syndrome would help to clarify the issue.

MATERIALS AND METHODS

Thirty-six patients with Sjögren’s syndrome were studied. The diagnosis was based on the presence of the following findings: xerostomia (decreased parotid flow rate); keratoconjunctivitis sicca (slit-lamp examination); and a focal lymphocyte infiltrate on minor salivary gland biopsy. All patients had Sjögren’s syndrome alone (primary) without clinical or serologic evidence of another connective tissue disease. All of these patients underwent clinical, roentgenologic, functional, and, in five cases, histologic evaluation of the respiratory system.

Clinical evaluation included a respiratory questionnaire modified from that of the British Medical Research Council and a physical examination. Roentgenologic evaluation included a posteroanterior chest roentgenogram. The roentgenograms were evaluated by two of us (S. H. C. and H. M. M.).

Functional evaluation included (Transfer screen II, Erich Jaeger, West Germany) the following: (1) spirometric tests of forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁); (2) flow-volume curves with recording of the expiratory flow-volume curve and maximum flow at 75 percent, 50 percent, and 25 percent of vital capacity (MEF75, MEF50, and MEF25); (3) total lung capacity (TLC) with the helium-dilution technique; and (4) carbon monoxide diffusing capacity (Dco) using the single-breath technique.

Five patients had transbronchial lung biopsy through a fiberoptic bronchoscope (Olympus BF-ITR).

RESULTS

Three of our patients were men, and 33 were women (ages 33 to 80 years; mean, 52.5 years), with onset of disease between 1 and 20 years (mean, 5.9 years) prior to respiratory evaluation. Extraglandular manifestations (eg, Raynaud’s phenomenon; splenomegaly; lymphadenopathy; purpura) were evident in 19 patients (52 percent). Only two patients were smokers (one man and one woman). The clinical respiratory evaluation showed that cough was a very frequent symptom (18/36 patients; 50 percent). This symptom varied in intensity from a foreign body sensation in the pharynx with minimal dry cough to exhaustive dry cough ending in vomiting. Only one patient had a productive cough. Exertional dyspnea was present in ten patients, thus being the second most common symptom. Two patients had a history of frequent respiratory infections. Bibasilar rales were present in ten patients. The positive roentgenologic findings included fine reticulonodular pattern in 15 patients and right hilar adenopathy in one. There were no patients with clinical or roentgenologic evidence of present or past pleural effusion.

The pulmonary functional evaluation showed that four patients had an FVC less than 80 percent of predicted, and five had an FEV₁ less than 80 percent of predicted, TLC, and seven had Dco less than 80 percent of predicted.

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values. Finally, 16 patients had MEF25 less than 65 percent of predicted. In eight of the 16 patients, this was their only functional abnormality, and their flow-volume curve was suggestive of small airways disease (Fig 1). In the other eight of the 16 patients, the diminished MEF25 was combined with diminished FVC, FEV1, TLC, or Dco alone or in combination and thus could not define small airways disease. All five transbronchial lung biopsies showed abnormal pulmonary tissue, ranging from parabronchial inflammation to lymphocytic interstitial infiltrates and diffuse interstitial fibrosis (Fig 2 and 3).

Using only objective criteria (functional, histologic), we grouped our patients with abnormal findings as follows:

**Group 1**

This includes nine patients (25 percent with evidence of diffuse interstitial pulmonary disease as evidenced by impaired Dco (7/7 tested) or compatible histologic findings (4/4 tested) or both (four patients). An additional patient (patient 8) had a restrictive ventilatory pattern with normal Dco. This patient had clinical and roentgenologic findings compatible with interstitial pulmonary disease.

**Group 2**

Three patients (8 percent) had obstructive ventilatory patterns (diminished FEV1 and MEF25 with normal FVC and TLC).

**Group 3**

Eight patients (22 percent) had evidence of small airways disease (diminished MEF25 with normal FEV1, FVC, TLC, and Dco).

To these three groups, we added a fourth based on clinical criteria without functional equivalent, namely:

**Group 4**

Six patients (17 percent) had normal functional evaluation but had a characteristic symptom, dry cough of varying intensity. One of these patients underwent bronchoscopic examination for this cough. The only finding was dry mucosa of the tracheobronchial tree. We have named this combination of cough and dry respiratory mucosa, "xerotrachea."

Adding up all four groups, we see that 27 of our patients (75 percent) had objective or definite clinical evidence of involvement of the respiratory system.

The chest roentgenogram was considered a subjective method of studying the pulmonary interstitium. It is characteristic that out of 15 patients with a roentgenogram suggesting interstitial pulmonary disease, three had functional evidence of large airways obstruction, four had small airways disease,
one had xerotrachea, and one had all other criteria negative for respiratory involvement. This poor correlation between a chest roentgenogram suggestive of interstitial pulmonary pathologic abnormalities and pulmonary function studies has been reported repeatedly.8,9

Correlation of the respiratory manifestations with other manifestations of Sjögren’s syndrome revealed that (1) extraglandular findings, other than respiratory, were present in five of nine patients without respiratory involvement and 15 of 27 patients with respiratory involvement \( (\chi^2 = 0); \) (2) rheumatoid factor was present in five of nine patients without and 13 of 27 patients with respiratory involvement \( (\chi^2 = 0.14); \) (3) antibodies to Ro(SSA) antigens were present in two of nine patients without respiratory involvement and eight of 27 with respiratory involvement \( (\chi^2 = 0.18) \) and antibodies to La(SSB) antigens in three of nine and eight of 27 patients, respectively \( (\chi^2 = 0.04); \) (4) the mean age of the patients with respiratory manifestations was 52.4 years, and they had symptoms related to Sjögren’s syndrome for a mean time of 5.9 years \( (\text{the respective mean values for patients without respiratory manifestations were 52.7 years and 5.4 years}); \) and (5) respiratory symptoms, when present, occurred in five patients before, in ten patients after, and in six patients concomitantly with the typical symptoms of Sjögren’s syndrome.

**Discussion**

In 1979, Hunninghake and Fauci10 in their review entitled "Pulmonary Involvement in the Collagen Vascular Disorders," suggested that this involvement is frequent in Sjögren’s syndrome and can be manifested as pleurisy, interstitial fibrosis, desiccation of the tracheobronchial tree, and lymphoid interstitial disease. They also stated that the first two could be manifestations of the concomitant rheumatic disorder and that only desiccation of the tracheobronchial tree and lymphoid interstitial disease are "specific" for Sjögren’s syndrome.

There have been several articles on the lungs and Sjögren’s syndrome since then. Only two deal with large populations of patients with primary Sjögren’s syndrome. Oxholm et al12 reported in their large series of 46 such patients that the most common functional abnormality was reduced pulmonary diffusing capacity. We have reported in a previous study of 22 patients with primary Sjögren’s syndrome4 that there are two distinct forms of respiratory involvement, ie, (1) "xerotrachea" manifested only by dry cough without any roentgenologic or functional abnormality, and (2) diffuse interstitial pulmonary disease. Pulmonary function in that study was evaluated only with spirometry and arterial blood gas levels. Three other studies deal with small numbers of patients with both primary and secondary Sjögren’s syndrome and stress airways obstruction as the most common abnormality.11,13

In this study, based on clinical, roentgenologic, functional, and histologic data, we suggest that primary Sjögren’s syndrome can frequently \( (75 \text{ percent}) \) involve the respiratory system from the trachea and large airways to the small airways, pulmonary parenchyma, and pulmonary interstitium.

Involvement of the trachea and large airways results in their desiccation and presents with dry cough that can, at times, be very annoying. We had patients treated for "asthma," "chronic bronchitis," or even "tuberculosis" because of this cough before Sjögren’s syndrome was diagnosed. We can attribute this isolated symptom of dry cough that was the only abnormal respiratory manifestation in six of our patients \( (17 \text{ percent}) \) to desiccation of the tracheobronchial tree ("xerotrachea"), since no other cause for the cough was found, and the desiccation of the airways was documented bronchoscopically. This has also been documented by other investigators in the past who have shown bronchial mucosal infiltration with mononuclear cells in similar patients.14,15 It is interesting that this group of patients cannot be detected with functional criteria, and therefore clinical evaluation is very valuable in their case.

Peripheral airways can be involved, and the result is frequent respiratory tract infections and obstructive ventilatory defects (three patients; 8 percent). In one such patient (patient 13), transbronchial lung biopsy revealed parabronchial chronic inflammation, probably secondary to repeated previous pulmonary infections. The medical history was suggestive, and the pulmonary function studies revealed obstruction of large airways.

Small airways \( (<2 \text{mm in diameter}) \) can also be involved \( (22 \text{ percent of our patients}; 8/36) \). This can be part of the interstitial pulmonary disease, as is well known for interstitial pulmonary disease of different etiology,14 but it can also occur alone. Thus, eight of our patients \( (22 \text{ percent}) \) had isolated small airways disease, manifested by significantly diminished MEF25 \( (<65 \text{ percent of predicted}) \) and suggestive flow-volume curves (Fig 1). Three patients had diminished MEF25 combined with impaired diffusion. This was considered part of the interstitial pulmonary involvement. Three more had diminished MEF25 combined with impaired FEV\(_1\). This was considered part of an obstructive ventilatory defect. Newball and Brahim15 have documented the abnormality of small airways in Sjögren’s syndrome histologically by showing "mononuclear cell infiltration around narrowed small airways" in two patients.

Diffuse pulmonary interstitial pulmonary disease was common in our patients \( (25 \text{ percent}; 9/36) \). This is in agreement with the large series of Strimlan et al1 and...
Oxholm et al but not with smaller series showing obstruction as the main abnormality. The lung biopsies that we performed on four such patients showed a spectrum of interstitial pathologic findings ranging from "active" lymphocytic infiltrates to interstitial fibrosis (Fig 2). Bronchoalveolar lavage should be very helpful for additional information of this involvement. It could also help to clarify if small airways disease is part of the interstitial pathologic abnormality or an isolated manifestation.

The correlation of respiratory manifestations with the clinical and serologic characteristics of Sjögren's syndrome showed that extraglandular manifestations and serologic markers, like antibodies to Ro(SSA) or La(SSB) antigens (or both), had similar frequency in patients with and patients without respiratory involvement. Finally, this correlation showed that respiratory symptoms occur often before or concomitantly with the first classic symptoms of Sjögren's syndrome. Thus, questions to detect dry cough should be included in the initial evaluation of patients with Sjögren's syndrome.

Our results indicate that respiratory involvement is frequent in patients with primary Sjögren's syndrome. The most common manifestations of this are diffuse interstitial pulmonary disease, small airways disease, and xerotrachea. Further studies are required, e.g., with bronchoalveolar lavage. These studies should include only patients with primary Sjögren's syndrome, thus avoiding the confusion of respiratory manifestations of the concomitant rheumatic disorder.

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