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Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjögren's syndrome

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ABSTRACT

Objective: Although high-resolution computed tomography (HRCT) is useful for the characterization of minute morphological changes in the lungs, no study has investigated risk factors for lung involvement detected by HRCT in patients with Sjögren's syndrome with or without respiratory symptoms. The aim of the current study was to investigate risk factors for lung involvement in patients with primary Sjögren's syndrome detected by HRCT, with a particular focus on airway and interstitial lung diseases.

Methods: We performed a retrospective cohort study of patients with primary Sjögren's syndrome and investigated risk factors for lung involvement detected by HRCT. A total of 101 patients with primary Sjögren's syndrome with initial HRCT examinations were enrolled.

Results: Higher age, dry mouth, and higher labial gland biopsy focus scores (≥4) were risk factors for airway diseases (odds ratio [OR] 1.064 confidence interval [CI] 1.026–1.102, OR 8.795 CI 2.317–33.378 and OR 3.261 CI 1.100–9.675, respectively) in the multivariable analysis. Higher age, male sex, and higher labial gland biopsy focus scores (≥4) were risk factors for interstitial lung diseases (OR 1.078 CI 1.032–1.127, OR 12.178 CI 1.121–132.307 and OR 3.954 CI 1.423–10.987, respectively) in the multivariable analysis. The presence of anti-T-lymphotropic virus type 1 antibodies was significantly more common in patients with airway diseases.

Conclusions: This study showed significant associations of labial gland biopsy focus scores and dry mouth with pulmonary manifestations in patients with primary Sjögren's syndrome. Focus scores as well as dry mouth may reflect lymphoproliferative activity in the lungs in patients with primary Sjögren's syndrome.

1. Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function and is associated with lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands. In addition, SS can also affect extraglandular organ systems including the skin, lung, heart, kidney, and the neural and hematopoietic systems. Pulmonary manifestations are

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List of abbreviations used

ANA	anti-nuclear antibody
CIs	confidence intervals
CT	computed tomography
ESSDAI	European League Against Rheumatism Sjögren's syndrome disease activity index
HRCT	high-resolution computed tomography
HTLV-1	human T-lymphotropic virus type 1
IgG	immunoglobulin G
IQR	interquartile range
NSIP	nonspecific interstitial pneumonia
OP	organizing pneumonia
ORs	odds ratios
pSS	primary Sjögren's syndrome
RF	rheumatoid factor
SS	Sjögren's syndrome
UIP	usual interstitial pneumonia

among the most prevalent extraglandular complications [1]. The most typical manifestations are airway abnormalities and interstitial lung diseases. Airway diseases are characterized by diffuse lymphocytic infiltration of the airway [1]. The common manifestations of interstitial lung diseases are nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), and organizing pneumonia (OP) [1]. Patients with SS with pulmonary involvement have a lower health-related quality of life and increased risk of mortality [2,3]. However, the mechanisms of lung disease development in patients with SS are not fully clarified.

The diagnosis of lung involvement in SS is usually based on clinical symptoms and plain chest radiographic findings or supplemental investigations with pulmonary function tests, bronchoalveolar lavage, and histopathological analyses [1]. However, plain chest radiographs have low sensitivity with regard to detecting early lung involvement, whereas high-resolution computed tomography (HRCT) has proven to be more sensitive than plain radiography, pulmonary function tests, and clinical findings [4–8], even in asymptomatic patients. In addition, HRCT is also useful for the characterization of minute morphological changes in the lungs.

Smoking history, male sex, higher age, the presence of antinuclear antibodies (ANAs), anti-La/SS-B antibodies, anti-Ro/SS-A antibodies, lymphopenia, a history of Raynaud's phenomenon, digestive involvement, and a long course of disease progression have been reported to be associated with lung involvement in patients with SS [3,6,9–12]. However, in most previous studies, pulmonary involvement was defined as the presence of respiratory symptoms associated with altered pulmonary diagnostic test results. To the best of our knowledge, no study has investigated risk factors for lung involvement detected by HRCT in patients with SS with or without respiratory symptoms. In addition, while it has been reported that the pulmonary manifestations of SS mainly involve airway abnormalities and interstitial lung diseases [1], the risk factors for each abnormality remain unknown. It is also unclear whether what was previously reported as risk factors for pulmonary involvement, defined as the presence of respiratory symptoms associated with altered pulmonary diagnostic test results, is identical to the risk factors for airway abnormalities and interstitial lung diseases detected by HRCT. In addition to being of predictive value, the identification of risk factors for each condition could help clarify the mechanisms of development of each pulmonary abnormality in patients with SS.

The aim of the current study was to investigate risk factors for lung involvement detected by HRCT in patients with primary SS (pSS), with a particular focus on risk factors for airway and interstitial lung diseases.

2. Materials and methods

2.1. Study population and covariates

This study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Nagasaki University Hospital (approval number: 16020823) and the University Hospital of Occupational and Environmental Health (approval number: H27-228). Informed consent was not required for the retrospective review of patient records, pursuant to the ethical guidelines of the Japanese Ministry of Health, Labour, and Welfare. We performed a retrospective cohort study of consecutive patients with pSS who visited Nagasaki University Hospital, Nagasaki, Japan or the University Hospital of Occupational and Environmental Health, Kitakyushu, Japan, from April 2008 to December 2015. SS was diagnosed based on the classification criteria of the American-European Consensus Group [13] 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 showing lymphocyte foci, test results indicating impaired salivary gland function, and the presence of autoantibodies (anti-Ro/SS-A, anti-La/SS-B, or both). Definite diagnosis of SS required the presence of any four of the six items, with histopathological findings or autoantibodies being one of the four items, or the presence of any three of the four objective criteria items. Collagen vascular diseases other than SS were excluded based on the absence of sufficient characteristic findings to meet the classification criteria for other collagen vascular diseases. Patients with initial HRCT evaluations were included in the final analysis. Data regarding patient characteristics were collected from clinical notes recorded at the time of initial pSS diagnosis, and included age, sex, smoking history, symptoms, and pathological findings of labial gland biopsies. Data regarding serum ANAs, rheumatoid factor (RF), anti-Ro/SS-A antibody, anti-La/SS-B antibody, anti-human T-lymphotropic virus type 1 (HTLV-1) antibody determined by chemiluminescent enzyme immunoassay, immunoglobulin G (IgG) levels, and European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI) [14] were also collected from the clinical notes recorded at the time of diagnosis.

2.2. Evaluation of chest radiography and HRCT findings

Chest radiographs and HRCT scans were interpreted independently and in random order by two pulmonologists without knowledge of the clinical status of the patients. Following the initial independent evaluations, divergent observations were resolved by consensus after consultation between the two observers. The pulmonologists recorded the following features seen on HRCT: (A) Features suggestive of airway diseases, including centrilobular nodules, bronchiectasis, and bronchial wall thickening. (B) Features suggestive of interstitial lung diseases, including ground-glass attenuation, consolidation, reticulation, and subpleural honeycombing. Interstitial lung diseases were categorized into three previously established patterns [15]: NSIP, UIP, and OP. After completion of the evaluation of HRCT, the findings that were judged to be due to pulmonary comorbidities, such as pulmonary infections, based on the clinical notes recorded by the attending physicians were excluded from the final analysis.

2.3. Determination of the focus scores in labial gland biopsies

Focus scores in labial gland biopsies were determined as previously described [16]. Briefly, the focus scores in labial gland biopsies were