CHEST

Original Research

INTERSTITIAL LUNG DISEASE

Minor Salivary Gland Biopsy To Detect Primary Sjögren Syndrome in Patients With Interstitial Lung Disease

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Purpose: **To describe a cohort of patients who presented with interstitial lung disease (ILD) of unknown cause, features of primary Sjögren syndrome (pSS), and a positive minor salivary gland biopsy (MSGB).**

Methods: **Thirty-eight patients with ILD evaluated at our center underwent an MSGB to confirm a diagnosis of pSS. All of the samples were reviewed by pathologists experienced in the evaluation of salivary gland histology. We defined a positive MSGB finding as a lymphocyte focus score of >1.**

Results: **At presentation, all patients had ILD, and symptoms of cough and dyspnea. None had a definable connective tissue disease (CTD) or known cause for their ILD. Thirteen patients (34%) had positive MSGB findings. Of these, the median age was 61 years (age range, 33 to 75 years); 7 patients (54%) were women; 8 patients (62%) had a smoking history; and 10 patients (77%) had sicca symptoms. In all patients, a thoracic high-resolution CT scan evaluation demonstrated bibasilar, peripheral-predominant, ground-glass, and reticular opacities. Four patients (31%) were negative for both antinuclear autoantibody (ANA) and rheumatoid factor (RF) autoantibody, and three patients (23%) were negative for ANA, RF, Sjögren syndrome (SS)-A, and SS-B autoantibodies. No patients experienced any complications from the MSGB. The identification of underlying pSS did not affect the management of ILD in these patients.**

Conclusions: **Confirming a diagnosis of pSS-related ILD by performing MSGB allows for a more precise CTD classification. This study provides evidence that CTD may exist subclinically, and longitudinal studies are needed to determine whether identifying occult CTD impacts on management, longitudinal changes in lung function, or survival.** ***(CHEST 2009; 136:1072–1078)***

Abbreviations: ANA = antinuclear autoantibody; CTD = connective tissue disease; HRCT = high-resolution CT; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; MSGB = minor salivary gland biopsy; NSIP = nonspecific interstitial pneumonitis; pSS = primary Sjögren syndrome; RF = rheumatoid factor; SS = Sjögren syndrome

Interstitial lung disease (ILD) comprises a diverse group of disorders characterized histologically by varying degrees of inflammation and fibrosis. Two major categories of causes for ILD include exposures (*eg*, aerosolized organic antigens, dusts, and drugs) and connective tissue disease (CTD).[1–3] Many ILDs have no identifiable etiology, including the idiopathic interstitial pneumonias (IIPs). The IIPs comprise a group of conditions with similar clinical, radiologic, and physiologic findings but different histologic patterns seen in surgical lung biopsy specimens.[1] These histologic patterns are not specific to the IIPs and may be seen, for example, in specimens from patients with ILD related to underlying CTD.[4] Some

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data[5,6] have suggested that, for a given histologic pattern, CTD-related ILD has a more favorable prognosis than IIPs, arguing for the careful evaluation of patients presenting with an idiopathic ILD in an attempt to identify underlying CTD.

The recognition of CTD is particularly challenging when ILD is its first or lone manifestation or when the extrathoracic features of CTD are subtle.[7] Attempts to identify underlying CTD often include a thorough history, physical examination, and serologic assessment for the presence of autoantibodies (*eg*, antinuclear autoantibody [ANA] and rheumatoid factor [RF]). Rheumatologic consultation may be sought, yet it is unclear whether these attempts are sufficient or whether additional testing is useful or necessary to identify the presence of CTD.[7]

Sjögren syndrome (SS) is one of the CTDs associated with lung abnormalities including ILD.[3,8–20] SS is a systemic autoimmune disease that is characterized by lymphocytic infiltration of exocrine glands, resulting in progressive atrophy, reduced secretions, and mucosal dryness (sicca syndrome). The term *primary SS* (pSS) refers to SS occurring in the absence of another definable CTD; *secondary SS* refers to SS occurring in the context of another definable CTD, such as rheumatoid arthritis. The prevalence of pulmonary abnormalities in patients with SS varies from 9 to 75%, depending on the inclusion of patients with primary or secondary disease and the sensitivity of the methods used to identify lung disease.[3,8–20]

Most authorities recognize the presence of focal chronic sialadenitis, as determined by minor salivary gland biopsy (MSGB), as a cornerstone in the diagnosis of pSS.[21–24] The most recent classification scheme for pSS[21] requires the presence of specific autoantibodies (SS-A [anti-Ro] or SS-B [anti-La]) or a lymphocytic focus score of ≥ 1 on the MSGB specimen in addition to measurable xerostomia or keratoconjuctivitis sicca. MSGB may be utilized to confirm a diagnosis when the clinical scenario suggests pSS. However, the utility of performing an MSGB to confirm a diagnosis of pSS in patients presenting with ILD is not known. The purpose of this study was to describe the clinical characteristics of patients who presented with ILD of apparently unknown etiology and underwent MSGB to confirm a diagnosis of pSS.

Materials and Methods

Patients

After obtaining institutional review board approval for this study, we identified 38 patients with ILD of unknown etiology who underwent MSGB as part of their comprehensive evaluation at National Jewish Health (formerly National Jewish Medical and Research Center) between 1999 and 2007. No patient presented with a definable CTD or other disease or exposure linked with ILD. As part of their ILD evaluation, all of the patients underwent a standardized assessment that included rheumatology consultation and extensive autoantibody testing. The decision to perform an MSGB was a clinical one that was made based on the recommendation of the rheumatologic consultation. A review of the medical records revealed that the following two main variables had prompted MSGB: the presence of sicca (keratoconjuctivitis sicca or xerostomia); or an elevated level of pSS-associated autoantibodies (*ie*, ANA, SS-A, SS-B, or RF) without features of another definable CTD.

Histopathology Review

The technique used to perform the MSGB was at the discretion of the surgeon performing the biopsy. All of the specimens were reviewed by two experienced pathologists (C.D.C. and S.D.G.) who were blinded to the clinical information. The focus score in a given area of glandular tissue was defined as the number of aggregates of ≥ 50 lymphocytes per 4 mm^2 of salivary gland tissue.[21–24] Some patients also underwent surgical lung biopsy or transbronchial biopsy as part of their ILD evaluation; our pathologists (C.D.C. or S.D.G.) reviewed slides from the biopsies to determine the predominant histologic pattern.

High-Resolution CT Scan Review

Two experienced thoracic radiologists (H.S. and D.A.L.), who were blinded to the clinical information and histopathologic diagnoses, reviewed the chest high-resolution CT (HRCT) scan images of each patient. The HRCT scan that had been performed closest to the MSGB date was chosen for review. The radiologists reviewed the HRCT scans and gave an opinion on the predominant radiographic pattern present, as previously described.[25]

pSS Diagnostic Criteria

The diagnosis of pSS was based on criteria accepted by the American-European Consensus Group.[21] These criteria require the confirmation of the presence of ocular and oral dryness combined with objective confirmation of autoimmunity as demonstrated by a positive MSGB finding (focus score ≥ 1) or positive reaction to anti-Ro (SS-A) or anti-La (SS-B) autoantibodies. As such, to make a definitive diagnosis of pSS, the presence of sicca is a requirement. In this retrospective cohort, we considered patients with positivity reactions for pSS-associated antibodies (ANA, SS-A, SS-B, or RF) along with a positive MSGB finding (focus score > 1) to have clinical features that were strongly suggestive of SS (*ie*, probable pSS).

A focus score of > 1 is a consistent finding in patients with SS and is considered the histopathologic cornerstone for a diagnosis of pSS.[21–24] As a focus score of exactly 1 may represent an early or mild form of pSS,[26] we chose to define a positive MSGB finding as a focus score of > 1. Quantitative assessment for keratoconjuctivitis sicca by Schirmer test was performed by the treating physician, and a positive result for the Schirmer test was defined as ≤ 5 mm of filter paper wetting at 5 min.

Statistical Analysis

We assessed intergroup (positive vs negative MSGB finding) differences by using *t* tests for continuous variables and a χ^2 test or Fisher exact test (where appropriate) for categorical variables. An $\alpha \leq 0.05$ was considered statistically significant. All of the