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

Table 1—*Clinical Characteristics*

Characteristics	Positive MSGB Finding (n = 13)	Negative MSGB Finding (n = 25)
Age, yr	61 (33–75)	63 (33–88)
Female gender	7 (54)	18 (72)
Smoking history	8 (62)	9 (36)
Raynaud syndrome	2 (15)	1 (4)
Arthralgias/arthritis	10 (77)	12 (48)
GERD	8 (62)	20 (80)
Keratoconjuctivitis sicca	8 (62)	17 (68)
Xerostomia	10 (77)	17 (68)
Positive Schirmer test result	6/7 (86)	9/10 (90)
ppFVC	75 (51–103)	60 (32–108)
$ppFEV_1$	79 (31–116)	63 (28–117)
ppDLCO	63 (49–89)	55 (23–86)

Values are given as median (range) or No. (%). GERD = gastroesophageal reflux disease; ppFVC = percent FVC; $ppFEV_1$ = percent predicted FEV_1; ppDLCO = percent predicted diffusing capacity of the lung for carbon monoxide.

data analyses were performed using a statistical software package (SAS, version 9.1.3; SAS Institute; Cary, NC).

Results

Patient Characteristics

All 38 patients presented with either cough (85%) or dyspnea (77%), and pulmonary function testing demonstrated reduced FVC and diffusing capacity of the lung for carbon monoxide (Table 1). All of the patients were evaluated by rheumatology as part of their ILD evaluation, and none had identifiable features that defined a specific CTD.

Thirteen patients (34%) had a positive MSGB finding (Fig 1), with focus scores ranging from 2 to 7. The clinical characteristics of the 13 patients with a positive MSGB finding and those of the 25 patients with a negative MSGB finding can be found in Tables 1 and 2.

Of those patients with a positive MSGB finding, the median age at biopsy was 61 years (age range, 33 to 75 years); seven patients (54%) were women, and eight patients (62%) had smoked cigarettes in the past. Symptoms of either keratoconjuctivitis sicca or xerostomia were present in 10 patients (77%), and the Schirmer test result was positive in six of the seven patients in whom it was performed. Eight patients (62%) were positive for ANA (three at a titer $< 1{:}160$, and five at a titer $> 1{:}160$), and three patients (23%) were positive for the RF antibody. Of the eight patients who were positive for ANA, six were also positive for SS-A, and two of these six patients were positive for SS-B as well. Two patients were positive for SS-A at a high titer but were negative for ANA. No other autoantibodies were detected. Four patients (31%) were negative for ANA and RF antibodies, and three patients (23%) were negative for ANA, RF, SS-A, and SS-B antibodies. Interestingly, the only difference between these two cohorts is that patients with a positive MSGB finding were more likely to be positive for SS-A antibody than were patients who had negative MSGB findings ($p = 0.03$). No patients experienced any complications from undergoing the MSGB. In this regard, the presence of a positive Schirmer test result was not of help in distinguishing the groups and supports the concept that MSGB provides added value for diagnosis.

All of the patients with a positive MSGB finding were considered to have pSS by their treating physicians. Ten of 13 patients (77%) with a positive MSGB finding met the formal criteria for the diagnosis of pSS.[21] The three other patients with a positive MSGB finding did not meet the formal

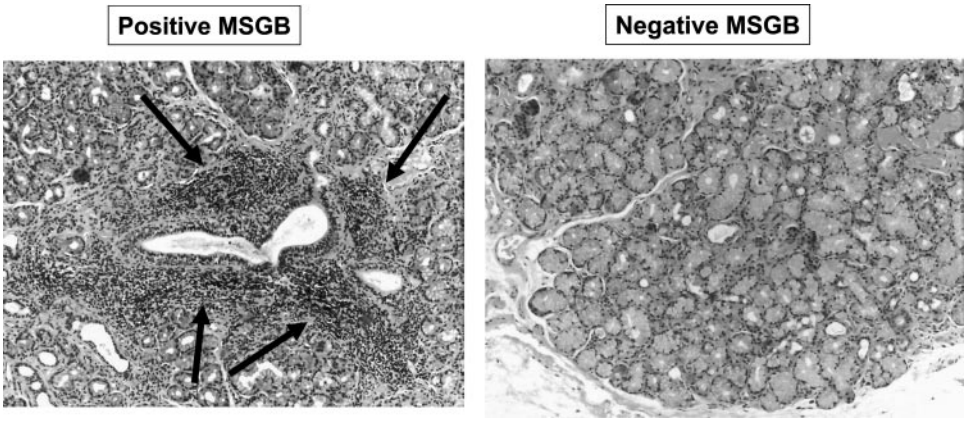

Figure 1. MSGB specimen demonstrating focal sialedinitis (hematoxylin-eosin, original × 10). *A*: arrows demonstrate cellular infiltration. *B*: comparison with a negative biopsy specimen.

Table 2—*Serologic Characteristics*

Characteristics	Positive MSGB Finding (n = 13)	Negative MSGB Finding (n = 25)
Erythrocyte sedimentation rate, mm/h	18 (1–63)	28 (1–122)
CRP, mg/dL	0.3 (0.1–2.2)	0.4 (0.4–11.1)
IgA mg/dL	354 (64–535)	201 (7–694)
IgG mg/dL	1,290 (629–3,400)	1,170 (786–4,950)
IgM mg/dL	113 (58–232)	109 (35–481)
ANA-positive	8 (62)	13 (52)
SS-A-positive*	8 (62)	6 (24)
SS-B-positive	2 (15)	1 (4)
RF-positive	3 (23)	2 (8)
Seronegative for ANA, SS-A, SS-B, and RF antibodies	3 (23)	6 (24)

Values are given as the median (range) or No. (%). CRP = C-reactive protein.
*p = 0.03.

criteria for the diagnosis of pSS as they lacked sicca symptoms; however, the combination of focal sialadenitis and the presence of autoantibodies (ANA, one patient; SS-A, two patients) provided strong support for a diagnosis of pSS. Immunomodulatory therapy was initiated in six of those patients (46%) with a positive MSGB finding, and in nine of those patients (36%) with a negative MSGB finding.

Transbronchial and Surgical Biopsies

Four of the 13 patients with positive MSGB findings had undergone transbronchial biopsies. Nonspecific chronic inflammation was noted in all of these patients. Additionally, one patient had a nonnecrotizing granulomata. Three of the 13 patients had undergone surgical lung biopsies. Lymphocytic bronchiolitis, nonspecific interstitial pneumonitis (NSIP), and chronic eosinophilic pneumonia were the histologic patterns identified.

Thoracic HRCT Scans

Each patient with a positive MSGB finding had thoracic HRCT scans available for review. All of the patients had varying degrees of ground-glass opacities and reticular abnormalities in a peripheral- and lower-lobe-predominant pattern consistent with ILD. Traction bronchiectasis was noted in nine patients, and honeycombing was noted in two patients. Nine patients had a lung injury pattern suggestive of NSIP; two patients had features of bronchiolitis with bronchiectasis, and one patient each had usual interstitial pneumonia and chronic eosinophilic pneumonia.

Discussion

Thirty-eight patients with ILD of unknown cause underwent comprehensive assessment that included pulmonary and rheumatology evaluation and detailed autoantibody testing. All patients underwent an MSGB to further investigate the clinical features suggestive of pSS. In 13 patients, the MSGB finding was positive, confirming a diagnosis of pSS. The cohorts of patients with positive and negative MSGB findings were similar, with the only difference being a higher percentage of anti-SS-A positivity in those patients with positive MSGB findings. Close to one-quarter of those patients with a positive MSGB finding were negative for autoantibodies. The performance of an MSGB led to the confirmation of pSS in a sizeable minority of our cohort (34%) and allowed for more precise classification of the ILD. However, the presence of a positive MSGB finding did not impact on management decisions in this retrospective cohort as similar proportions of patients in each cohort were treated with immunomodulatory therapy. Nonetheless, it may impact on issues of prognosis, given the better outcome in patients with CTD-associated diffuse lung disease. In addition, the more precise ILD classification also may have implications for future management strategies that might differ from those employed for idiopathic disease.

A variety of pulmonary abnormalities, including ILD, airways disease, and vascular disease, are associated with SS[7–19] (see the comprehensive review by Quismorio[19]). The frequency of specific pulmonary abnormalities associated with pSS in published studies[7–19] is variable. This variability is due to several factors, including the lack of uniform diagnostic criteria for SS, differing modalities to define pulmonary abnormalities, the variability in the number of current or former smokers and the possible presence of smoking-related lung disease, and the inclusion of patients with pSS or secondary SS.[19] Investigations combining both pSS and secondary SS are particularly difficult to interpret because of concerns that any associated pulmonary abnormality could be due to the primary CTD (*eg*, rheumatoid arthritis) rather than to secondary SS.

Since the American Thoracic Society/European Respiratory Society consensus statement[1] for the revised classification of IIPs, NSIP has been reported[14,18] to be the predominant lung injury pattern in pSS. Ito et al[14] described the histopathologic patterns seen on surgical lung biopsy specimens from 33 patients with pSS. NSIP was identified in 20 patients (61%), 19 of whom had fibrotic NSIP. Other patterns identified included bronchiolitis (n = 4), lymphoma (n = 4), atelactatic fibrosis (n = 2), amyloid (n = 2), and

honeycomb lung (n = 1).[14] HRCT scan pathologic correlation resulted in a 94% positive predictive value of a CT scan NSIP pattern for the pathologic diagnosis of NSIP. In the cohort of Ito et al,[14] the mean age was 56 years, 82% of the patients were women, 69% of the patients were positive for ANA, 67% of the patients were positive for SS-A, and 27% of the patients were positive for SS-B.

Parambil et al[18] evaluated the histologic patterns on surgical or transbronchial lung biopsy specimens from 18 patients with pSS[18] and found NSIP (n = 5), organizing pneumonia (n = 4), usual interstitial pneumonia (n = 3), lymphoid interstitial pneumonia (n = 3), lymphoma (n = 2), and amyloidosis (n = 1). In their cohort, the median age was 62 years, 83% of the patients were women, 100% of the patients were positive for ANA, 94% of the patients were positive for SS-A, 50% of the patients were positive for SS-B, and 82% of the patients were positive for RF. Although details are provided regarding the abnormalities noted on HRCT scans (*eg*, ground-glass opacities, irregular reticular opacities, and airspace consolidation), there was no HRCT scan-rendered diagnosis, and thus, a CT scan-pathologic correlation is not available.

On average, the characteristics of the patients who were confirmed to have pSS-related ILD in our cohort were similar to those of the patients in each of these two prior studies.[14,18] The predominant HRCT scan pattern seen in our cohort was suggestive of an underlying histologic pattern of NSIP. Like the other studies, biopsy specimens in the current study revealed various airways and ILD injury patterns, and demographic and serologic data were broadly similar. Interestingly, three of the patients in our cohort with positive MSGB findings were seronegative for ANA, SS-A, SS-B, and RF. Despite being autoantibody-negative, each patient had symptoms and signs of xerostomia and keratoconjuctivitis sicca, and lymphocyte focus scores on MSGB specimens of ≥ 1. Most of our MSGB-positive cohort (77%) met the current consensus criteria for the diagnosis of pSS.[21] The remaining patients did not meet the current criteria because of the absence of confirmed sicca symptoms. Despite the lack of sicca, the results from the MSGB combined with autoantibody positivity in these patients strongly supported a diagnosis of pSS.

To increase specificity, we chose to increase the threshold for a positive MSGB finding to a focus score of > 1. The current consensus criteria for pSS define a positive MSGB finding as a specimen having one or more aggregates of ≥ 50 lymphocytes in 4 mm^2 of salivary gland tissue (*ie*, lymphocyte focus score of ≥ 1).[21] Since 1966, when MSGB findings were first linked to SS, several thresholds have been proposed.[23,24] A focus score of exactly 1 may represent an early or mild form of SS, and some have argued[26] that it should not be used as the diagnostic criterion for SS. In contrast, a focus score of > 1 is a consistent finding in patients with SS and is considered by many authorities[21–24] to be the histopathologic cornerstone for a diagnosis of SS.

Caporali et al[22] recently reported on the utility of MSGB in a cohort of 452 patients with suspected SS, of whom 124 were confirmed to have pSS according to revised consensus criteria,[21] using a lymphocyte focus score of ≥ 1. Among those patients who were confirmed to have pSS, 97% had xerostomia, 93% had xerophthalmia, 91% were positive for ANA, 69% were positive for RF antibody, 81% were positive for SS-A antibody, and 30% were positive for SS-B antibody. They confirmed that MSGB is a simple, safe, and reliable tool for the diagnosis of pSS.[22]

In contrast, however, there are authorities[26] who have questioned the overall utility of MSGB in general. Radfar et al[27] have reported that 15% of healthy individuals may have a positive MSGB finding, arguing that focal sialadenitis may occur in the absence of SS. It appears that the optimal diagnostic criteria for SS remain unresolved, and the precise role of MSGB in the evaluation of SS has not been accepted universally.[26,28]

It is common practice to evaluate for an underlying CTD when confronted with a patient with new-onset ILD.[3,4,7] There are numerous implications for identifying an underlying CTD; most significantly, CTD-ILD may be associated with a more favorable prognosis than idiopathic ILD.[5,6] That being said, it is not known whether the identification of more subtle, or occult, forms of CTD carries a similarly more favorable prognosis. It is not known whether confirming pSS with MSGB impacts on either the management or prognosis of ILD patients, although in general the association of diffuse lung disease with CTD is more favorable. In our retrospective cohort, the confirmation of pSS-related ILD by MSGB did not impact on management decisions, as roughly equal percentages of patients among those with a positive or negative MSGB findings received immunomodulatory therapies. Nonetheless, it can be argued that future decisions that incorporate the knowledge of a likely presence of CTD might well impact on treatment choices, given the better prognosis for CTD patients. Clearly, more studies are needed to better determine whether diagnosing an occult CTD, such as pSS, among patients with ILD impacts on therapy or prognosis.

As for the patients with a negative MSGB finding, they are difficult to further characterize. Despite a comprehensive evaluation, we were unable to ascribe a specific diagnosis in these patients. Some investigators[29] have suggested that the finding of

NSIP alone merits consideration for the presence of an undifferentiated CTD. Indeed, among our patients with negative MSGB findings, the female predominance (72%), autoantibody positivity (60% of patients with positive for ANA or RF autoantibody), and NSIP predominance (60%) are all features associated with CTD. Some patients had variable extrapulmonary features suggestive of an evolving CTD, and eight patients (32%) had a lymphocyte focus score of 1 on MSGB specimen. As discussed above, this could represent an early or mild salivary component of pSS. Although our suspicion is that the conditions of many of these patients likely will evolve into a defined CTD, without more definitive evidence for CTD we considered them to remain undefined. In this study, many of these patients were treated with immunomodulatory therapies that were similar to the approach used in patients with known CTD-related ILD.

Although the identification of pSS by MSGB apparently had no impact on treatment decisions, the positive MSGB finding allowed a more specific diagnosis to be made, and this more precise classification suggests a prediction of a better outcome for these patients than for those with idiopathic disease. Instinctively, more precise diagnoses are desirable, and confirming a diagnosis of pSS-related ILD is important in this context. That it did not impact on the decision to use immunomodulatory therapies in this retrospective study has been recognized. However, future management decisions that need to incorporate a variety of factors could well be influenced by the knowledge that a patient with a well-defined CTD has a better prognosis than that for a patient with an idiopathic counterpart.

This study has limitations. The small sample size and referral center bias may influence external validity. As with any retrospective study, the lack of systematic decision making, data collection, and outcome assessment may introduce bias. Quantitative assessment for keratoconjuctivitis sicca was not performed in all patients, and no quantitative assessment for xerostomia was performed. Biopsy of a minor labial salivary gland is an inexpensive and low-risk procedure. However, it does require an experienced surgeon (we recommend an otolaryngologist or odontologist who is experienced in the technique), and no specific protocol or technique was uniformly followed by the surgeon performing the biopsy. We were also limited by the diagnostic confusion and lack of consensus agreement surrounding the classification of pSS.[26,28] The lack of follow-up data to determine whether there was indeed a prognostic impact for a positive MSGB finding is a significant limitation as well, even though patients with CTD-associated lung disease generally have a better outcome. Although the management of these patients did not appear to be affected by the confirmation of pSS, future studies might confirm a more favorable outcome.

In conclusion, we have described a cohort of patients who presented with ILD of unknown cause who were confirmed to have pSS based on a comprehensive evaluation that included performing an MSGB. Even though the confirmation of pSS by the MSGB allowed for the more precise classification of patients with an undefined ILD, this classification did not impact the management of these patients. Although the procedure was well tolerated in our cohort, MSGB is invasive and does have potential for associated risk.[26] Based on the current evidence, we cannot advocate more widespread use of MSGB in clinical practice, but we would advocate for prospective studies to determine whether the identification of occult CTD, such as with the confirmation of pSS by MSGB, has an impact on treatment choices, longitudinal changes in lung function, and overall prognosis.

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