Standardisation of labial salivary gland biopsies in Sjogren's syndrome: importance for the practicing rheumatologist

Robert I Fox

Although only a small number of rheumatologists participate in clinical trials of Sjogren's syndrome (SS), the majority of rheumatologists need to assess the new criteria for SS in their clinical practice. We need to know how to obtain and evaluate the minor labial salivary gland (LSG) biopsy. We are increasingly asked to make critical therapeutic decisions about treatment of life-threatening clinical situations that might be due to SS, so uniform criteria for correct diagnosis are increasingly important.

Fisher *et al*¹ present an expert consensus for 'standardisation of LSG' histopathology in clinical trials in primary SS in this issue.

Rheumatologists are aware that a 'new' consensus criteria between the American College of Rheumatology and European League Against Rheumatism were recently approved.² However, it is less well recognised that SS diagnosis is now based on a 'point system', and that four points are required for diagnosis of SS.

- ▶ A *positive labial salivary biopsy (LSB)* only qualifies for three points (table 1). Thus, a positive LSB will not fulfil criteria alone.
- ▶ Similarly, a *positive antibody to Sjogren's Syndrome A (SS-A)* only counts for three points, and alone, will not fill criteria.

Thus, the basis for diagnosis and treatment of our most difficult patients, such as those that lack antibody to SS-A, depends on the LSG biopsy. This article deals with the methods of acquisition of tissue and histological interpretation of the LSB.

The consensus report on LSG represents the outcome of a 2-day workshop held in Birmingham, UK in 2014. This group included rheumatologists, pathologists, healthcare statisticians and three patients (since repeat LSB may be

reported in clinical study outcome and patient input important).

Calculation of focus size, additional histopathological features of prognostic importance, reporting standards and requirements of placebo groups were discussed. Delphi process was then conducted using a group of 50 experts (including the original 20 participants) who rated 'agreement' on a 10-point scale. The process was repeated until 75% of respondents agreed on a score of seven or greater.

The consensus for important points in the evaluation of LSB is summarised in table 1 in the article by Fisher *et al*.¹ It presents some of the relevant points for the practicing rheumatologist.

These recommendations are graded from A (weakest) to D (strongest).

Also of importance, table 1 in the article by Fisher *et al*¹ shows the variability in 'weight of importance' in different pathologic features among experts.

One of the immediate points to recognise is that *the new consensus favours focus score (FS)* of Daniels *et al*^{3,4} rather than the older scoring method (class I–IV) of Chisholm and Mason.⁵

This is important—since many pathologists still report results based on the now outdated 'class score'. Rheumatologists need to remember that many pathologists read out a biopsy as 'no evidence cancer',

when the actual reason for the rheumatologist's biopsy was the diagnosis of SS.

Alternatively, a pathology report that a LSG was 'consistent with SS' means that the pathologist was probably not clearly informed that the biopsy needs to be 'graded' according to the new consensus criteria and that the biopsy should be re-evaluated according the guidelines submitted in this article.

Several points of importance to practicing rheumatologists

- ▶ At the initial stage of obtaining the biopsy, *the largest possible area to be sampled would give the best results*, but a reasonable compromise is *four glands*—although a minimum of evaluable surface area (8 mm²) may be achieved with 2–3 glands.
 - However, some glands may be atrophic or damaged, and the volume of material obtained at biopsy should be sufficient to overcome this artefact and achieve a valid result. This is also important when reviewing outside biopsies that may have been 'over read'.
- ▶ A key conceptual point is that *SS is a 'systemic' disease*, and the average of multiple different lobules needs to be evaluated, rather than concentration on a single abnormal lobule, which may not be typical of the entire gland.
- ▶ *FS score was preferred over focal lymphocyte score (FLS)*, since measurement of an infiltrated area avoids difficulties in determining whether to count partially confluent foci as one or two.
 - Also, the FS removes the arbitrary 'ceiling' score in case of more widespread confluence of infiltrates.
- ▶ An area of debate involved a previous suggestion of cutting 'multiple' levels of the same biopsy,⁶ since this introduces the bias of choosing the 'best' slide.
 - The consensus group favoured *evaluation of more lobules* rather than recutting the same lobule.
- ▶ *Germinal centres should be reported*, although there is need for a clear definition of these structures using only H&E.
 - For clinical trials, additional staining with CD21 (a marker of follicular dendritic cells) as well as CD20 and CD3 is required.
 - Pathologists were advised to use caution to avoid overestimating germinal centers (GCs) by relying solely on CD21.^{7,8}

The principal weakness of the study is its dependence on expert opinion. Ideally, diseases should be classified on the basis of their underlying pathogenesis rather than on their histopathological manifestations,

Table 1 Diagnosis of Sjogren's syndrome (SS) is now based on a weighted basis¹

Individuals with signs and symptoms suggestive of SS need at least four points to fulfil diagnostic criteria

LSG with FLS and FS≥1	3
Anti-SSA/B/Ro/La	3
OSS≥50.15	1
Schirmer ≤5 mm/5 min	1
UWS≤0.1 mL/min	1
Oral symptoms 0.9	–
Ocular symptoms 0.9	–

Labial salivary gland (LSG) with FLS and focus score (FS) ≥1, LSG with focal lymphocytic sialadenitis and FS≥1 foci/4 mm². OSS, ocular staining score; UWS, unstimulated whole saliva flow rate.

Correspondence to Dr Robert I Fox, Scripps Memorial Hospital-Ximed, Suite #911, 9850 Genesee Ave, #91, La Jolla, CA 92037, USA; robertfoxmd@icloud.com

but in the absence of the precise genetic and environmental factors, we need to have a uniform database for clinical and research studies.

SUMMARY

Rheumatologists have 'blindly assumed' that after their LSG biopsy disappeared into the Department of Pathology for 'evaluation', a magical 'Gold Standard' answer would emerge. When a patient has been seen at an outside institution and was told of a 'positive' biopsy, this information enters the medical history of the patient as an established fact. The LSG biopsy result must be reviewed (rather than relying on patient's history) and perhaps the LSG biopsy slide may need to be obtained and re-evaluated to confirm the diagnosis.

This article points out the *variability of interpretation of LSB* even among pathologists who have significant experience with SS.⁹

The variability among community pathologists who are not familiar with reading of LSB is likely to be much higher than that exhibited by the group of experts represented in this study.

We urge rheumatologists to pass these consensus guidelines to their pathologists and to clearly label all our LSB specimens as an evaluation for SS.

Further, this article should encourage rheumatologists to obtain LSG as part of diagnosis based on new criteria, and not simply rely on antibody to SS-A/Ro when important clinical decisions are at stake.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

CrossMark

To cite Fox RI. *Ann Rheum Dis* 2017;**76**:1159–1160.

Received 18 December 2016

Revised 14 January 2017

Accepted 6 February 2017

Published Online First 2 March 2017

► <http://dx.doi.org/10.1136/annrheumdis-2016-210448>

Ann Rheum Dis 2017;**76**:1159–1160.

doi:10.1136/annrheumdis-2016-210851

REFERENCES

- 1 Fisher BA, Jonsson R, Daniels T, *et al.* Standardisation of labial salivary gland histopathology

in clinical trials in primary Sjögren's syndrome. *Ann Rheum Dis* 2017;**76**:1161–8.

- 2 Shiboski CH, Shiboski SC, Seror R, *et al.* 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017;**76**:9–16.
- 3 Daniels TE, Whitcher JP. Association of patterns of labial salivary gland inflammation with keratoconjunctivitis sicca. Analysis of 618 patients with suspected Sjögren's syndrome. *Arthritis Rheum* 1994;**37**:869–77.
- 4 Daniels TE, Cox D, Shiboski CH, *et al.* Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. *Arthritis Rheum* 2011;**63**:2021–30.
- 5 Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* 1968;**21**:656–60.
- 6 Morbini PA, Manzo A, Caporali R, *et al.* Multilevel examination of minor salivary gland biopsy for Sjögren's syndrome significantly improves diagnostic performance of AECG classification criteria. *Arthritis Res Ther* 2005;**7**:1.
- 7 Jonsson MV, Skarstein K. Follicular dendritic cells confirm lymphoid organization in the minor salivary glands of primary Sjögren's syndrome. *J Oral Pathol Med* 2008;**37**:515–21.
- 8 Delli K, Haacke EA, Ihrler S, *et al.* Need for consensus guidelines to standardise the assessment of germinal centres and other histopathological parameters in salivary gland tissue of patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2016;**75**:e32.
- 9 Fisher BA, Brown RM, Bowman SJ, *et al.* A review of salivary gland histopathology in primary Sjögren's syndrome with a focus on its potential as a clinical trials biomarker. *Ann Rheum Dis* 2015;**74**:1645–50.