Reliability of histopathological salivary gland biopsy assessment in Sjögren’s syndrome: a multicentre cohort study

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Abstract

Objective. The aim of this study was to assess intraobserver and interobserver reliability of minor salivary gland biopsy (MSGB) in SS.

Methods. All MSGBs available from the Tolerance and Efficacy of Rituximab in Primary Sjögren’s Syndrome (TEARS) study were subjected to a standardized blinded assessment by a single specifically trained pathologist twice at a 2 month interval; both the Chisholm–Mason (CM) grade and the focus score (FS) were determined. Baseline histopathological reports by local pathologists at each study centre were compared with the first standardized blinded assessment. Agreement was assessed for the dichotomized FS (dFS) and dichotomized CM (dCM) grade, as well as for nine other histopathological features.

Results. Eighty-nine MSGBs were studied. Intraobserver κ values were 1 for dFS, 0.80 for dCM, 0.67 for germinal centre-like structures, 0.44 for fibrosis and 0.29 for confluent foci. Most of the local histopathological reports based their diagnosis on the CM grade, although the FS was often reported or the data needed to determine it were provided. Interobserver agreement κ values were 0.71 for dFS, 0.64 for dCM, 0.46 for focal lymphocytic sialadenitis, 0.42 for non-specific chronic inflammation and 0.16 for fibrosis.

Conclusion. Although FS reliability was good, disparities were noted in the assessment methods used by local pathologists. The protocol for FS determination was not followed routinely, with the result that the FS was often overestimated. Germinal centre-like structures, which predict lymphoma, showed good reliability but were inconsistently reported.

Key words: Sjögren’s syndrome, minor salivary gland biopsy, Chisholm, focus score, reliability.

Introduction

SS is a common chronic autoimmune disease characterized by lachrymal and salivary gland dysfunction due in part to lymphocytic infiltration and destruction of the gland parenchyma [1–5]. Diagnosis relies on a combination of clinical and laboratory findings, among which minor salivary gland biopsy (MSGB) abnormalities are a major criterion [6–9]. MSGB has been added to preliminary European classification criteria to improve their
diagnostic performance and to exclude other entities resembling SS [10, 11]. In 1968, Chisholm and Mason introduced an MSGB grading system with five grades [1], 0–4, based on the presence of diffuse lymphocytic infiltration and/or lymphocytic foci, with a focus defined as an aggregate of at least 50 lymphocytes. All aggregates were taken into account, whatever the aspect of the adjacent glandular parenchyma. The result was expressed as foci per 4 mm² of tissue. Greenspan and Daniels [12, 13] subsequently added the focus score (FS) concept, with the focus as the number of foci per 4 mm² of normal-appearing tissue. The presence of foci adjacent to apparently normal mucous acini defines focal lymphocytic sialadenitis (FLS), as opposed to non-specific chronic sialadenitis (NSCS), in which glands may have lymphocytic aggregates but also present acinar atrophy, fibrosis and dilated ducts. Other grading systems were suggested subsequently [14–16], generating debate about the best histological method for assessing MSGB. Nevertheless, FLS is strongly associated with the serological and ocular manifestations of SS [17] and an FS value \( >1 \) rather than \(<1\) [18]. Although still widely used, the Chisholm–Mason (CM) grading system fails to distinguish FLS from non-specific chronic sialadenitis, an inflammatory disorder that does not involve autoimmunity. Furthermore, sialadenitis and the FS can be challenging to evaluate even for experienced pathologists. In addition, the FS is not determined routinely by all pathologists, a fact that results in diagnostic discrepancies [19, 20]. Thus a blinded FS-based review of 60 MSGBs from 58 individuals resulted in revision of the initial diagnosis in 53% of cases, established previously undiagnosed SS in 12 patients and refuted a previous diagnosis of SS in 8 patients based on the work of Tavoni et al. [19]; in 58 patients, the initial evaluation had not involved FS determination. Other histopathological features sometimes found in MSGBs include germinal centre-like structures, which may predict lymphoma and deserve incorporation into severity classification systems for SS and monitoring criteria for specific patient subgroups [21–23].

Despite these uncertainties, a recent systematic review confirmed the good diagnostic value of MSGB, with sensitivity and specificity values ranging from 63.5% to 93.7% [24], but this article does not report the methods used to assess the MSGBs. Specificity cannot be perfect, since MSGB alterations are found in healthy elderly patients. Among 68 patients free of systemic disease and 12–78 years of age, 6 (8.8%) had FS values \( >1 \) [25, see Table 4]. Similarly, among 54 apparently healthy patients with a mean age of 31.5 years, 8 (14.8%) had FS values \( >1 \) [26]. The significance of these findings is unknown, but hypotheses include trauma, lip-biting habit, infections and early SS. An obstacle to the interpretation of published data is the use of various grading systems. Thus, of the nine studies identified in the above-mentioned systematic review [24], four used the CM scale, four used the Daniels scale and one used both. Achieving a consensus about a standardized method for obtaining, processing and assessing MSGB is crucial.

The primary objective of this study was to assess the intraobserver reliability of each histopathological criterion used to assess MSGBs. We also determined the level of agreement between the initial pathologist reports of MSGB findings and a centralized standardized evaluation by a pathologist specifically trained to assess MSGBs. To achieve this objective, we used data from the recently published randomized multicentre Tolerance and Efficacy of Rituximab in Primary Sjögren’s Syndrome (TEARS) study, designed to evaluate the efficacy of rituximab in primary SS [27].

**Patients and methods**

**Patients**

The TEARS study patients were recruited at 14 university hospitals in France if they fulfilled the new American-European Consensus Group (AECG) criteria for SS [6] and had active disease, defined as scores of at least 50 mm on at least two of four visual analogue scales (VASs) (from 0 = none to 100 = worst possible) for global disease, pain, fatigue and dryness. Additional requirements were either SS symptom onset within the last 10 years and biologically active SS [defined as autoantibodies (anti-Ro-SSA antibodies or RF), cryoglobulinaemia, hypergammaglobulinaemia, \( \beta_2 \)-microglobulin elevation or hypocomplementaemia] or systemic SS with at least one extraglandular manifestation or current parotid gland enlargement.

MSGB was performed routinely at 4 of the 14 participating centres (Brest, Lille, Nantes and Rouen) at study inclusion and after 24 weeks. The MSGB specimens were immediately fixed in formalin, processed and embedded in paraffin according to local standardized laboratory methods. MSGBs in paraffin blocks, the corresponding slides and the local pathologist reports were sent to the coordinating centre in Brest (Fig. 1). The TEARS study was approved by the appropriate ethics committee (CPP Ouest VI) and all patients gave written consent before study enrolment. The protocol is registered on ClinicalTrials.gov (NCT00740948).

**Training session**

Intraobserver and interobserver reliability of each histopathological feature was assessed by two of the authors—S.C., with 2 years of experience evaluating MSGBs, and I.O., with >20 years of experience evaluating MSGBs. The training session consisted of both observers evaluating 32 MSGBs from the Brest centre histopathology specimen bank (Brest). None of these 32 MSGBs were from TEARS study patients.

**Intraobserver reliability of MSGB review by a single trained pathologist at the study centre**

All MSGBs were read twice, 2 months apart, in random order by S.C., who used a standardized blinded procedure to evaluate 11 histopathological features. All slides were anonymized via the use of a random-number sequence.
The TEARS cohort included 93 minor salivary gland biopsies (MSGBs) from 60 patients, of which 89 were sent to the Brest coordinating centre and entered into the study and 77 had available baseline pathology reports. The first and second evaluations by a single trained pathologist at the Brest coordinating centre were done 2 months apart to assess intraobserver agreement. The first evaluation by this pathologist was compared with the baseline reports by the local pathologists at each centre to assess interobserver agreement.

**Interobserver reliabilities of baseline MSGB evaluations by local pathologists**

Baseline histopathological reports written by the local pathologists at the four study centres that performed MSGBs were sent to the coordinating centre and reviewed. The number of reports indicating the presence (coded 1) or absence (coded 0) of each feature was recorded. We considered the following seven features, which could be described using various synonyms: acinar depletion, acinar atrophy or acinar metaplasia; ductal hypertrophy, duct dilatation, ectasia or hyperplasia; NSCS, diffuse fibrosis, fibrous scar or sclerosing lymphocytic sialadenitis; fibrosis, perilobular fibrosis or intralobular fibrosis; and adiposis, fatty degeneration or fatty replacement.

To evaluate interobserver reproducibility, we compared the presence or absence of each of these seven features according to the local baseline histopathological reports and to a standardized review by S.C., who did not have access to the local baseline pathologist reports.

**Histopathological criteria**

The 11 histopathological features evaluated during the centralized reviews by S.C. and I.Q. are described below and in Fig. 2. The digital slide scanner NanoZoomer (Hamamatsu, Hamamatsu City, Japan) was used to digitize the slides and the biopsy surface areas were measured using the freehand surface area tool in NanoZoomer Digital Pathology Viewer software (Hamamatsu). This method ensures highly accurate standardized surface area measurement. The dichotomized FS (dFS) was defined as the lymphocytic FS as described by Greenspan and Daniels [24, 25] and at http://sicca.ucsf.edu (see http://sicca.ucsf.edu/LSG_bx_Grading_SOP.pdf) [17, 18], dichotomized by scoring values <1 as 0 and values ≥1 as 1. The dichotomized CM (dCM) grade was obtained by scoring CM grades [1] as 0 if equal to 0, 1 or 2 and as 1 if equal to 3 or 4. FLS was defined as the presence of one or more dense aggregates of ≥50 lymphocytes adjacent to apparently normal mucous acini located within lobes or lobules free of generalized duct dilation or fibrosis and containing few or no plasma cells, either in the absence of other evidence of inflammation or predominating markedly over any other evidence of inflammation. NSCS and sclerosing lymphocytic sialadenitis (intense NSCS) were included in a single category and defined as scattered or focal infiltrates of lymphocytes and macrophages that were not immediately adjacent to apparently normal acini and that were located within gland lobules, gland lobes or entire glands exhibiting some combination of mild to moderate acinar atrophy, interstitial fibrosis and dilated ducts, with these last often filled with inspissated mucus. Within-normal-limits glands were defined as normal architecture, densely arranged normal acini and scattered or small aggregates of plasma cells with few or no lymphocytes. Fibrosis was defined as collagenous fibrosis sheathing the ducts or forming tracts that dissociated the lobules and encased the acini. Duct dilatation was defined as a duct lumen enlargement with epithelial flattening. Acinar depletion (or atrophy) was defined as de-differentiation of the acinar epithelium and/or loss of gland parenchyma, with substitution by adipocytes or fibrosis. Adiposis was defined as the replacement of normal parenchyma by adipocytes. Germinal centre-like structures were defined as well-circumscribed mononuclear inflammatory cell infiltrates (≥50 cells) exhibiting a tightly packed dark zone and a more loosely packed light zone within an otherwise normal salivary gland epithelium [28]. Confluent foci were defined as focal lymphocytic infiltrates that were too large or numerous to be counted separately.

**Statistical analysis**

Statistical analysis was performed with SPSS version 22 (IBM, Armonk, NY, USA). Cohen’s $\kappa$ statistic was used to assess interobserver agreement while taking chance agreement into account [29]. The 95% CIs were computed. Values of $\kappa$ were interpreted as follows [28]: 0.81–1.00, almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; 0–0.20, slight agreement; −1.0–0, no agreement. The intra- and interclass correlation coefficients were computed to evaluate the quantitative variable of focus score. Bland–Altman plots were constructed to assess agreement between the CM grade and the Greenspan–Daniels FS [30]. Since the CM grade and the Greenspan–Daniels FS were dichotomized, we dichotomized the CM and the Greenspan–Daniels FS at the median value and calculated the sensitivity, specificity, positive and negative predictive values, and accuracy.
Fig. 2 Main histopathological features of minor salivary gland biopsies in patients with primary syndromes

Minor salivary gland biopsy stained with haematoxylin, eosin and saffron. (A) Normal parenchyma with mucinous acini. The cells have abundant cytoplasm with clear mucin (10×). (B) Dense aggregate of >50 lymphocytes defining a focus adjacent to mucous acini of normal appearance (10×). (C) Duct dilation (10×). (D) Focal lymphocytic sialadenitis (FLS) with at least five foci and confluent foci adjacent to mucous acini of normal appearance (4×). (E) Non-specific chronic sialadenitis (NSCS) with scattered infiltrates of lymphocytes and moderate acinar atrophy and interstitial fibrosis (10×). (F) Focal lymphocytic sialadenitis with a single prominent germinal centre-like structure (10×).
grade takes all the foci into account, we expect overestimation of the number of foci.

Results

Study population

Of the 122 TEARS study patients with primary SS, 60 underwent MSGB and were included in the present study. Of these 60 patients, 33 had two MSGBs at baseline and week 24, 23 had a single MSGB at baseline and 4 had a single MSGB at week 24. A total of 93 MSGBs, 89 biopsy specimens and their corresponding slides were sent to the Brest study coordinating centre and included in the present study. The specifically trained pathologist (S.C.), to avoid variability of evaluation between different levels of tissue, evaluated the same slides as the local pathologists. If multiple MSGB sections were available, the level with the higher FS was retained, as recommended [18, 31]. The mean FS in our 60 patients was 2.8/4 mm² and 31 of 60 patients (51%) had a FS ≥ 1.

Centralized histopathological assessment

Training session: interobserver agreement between the specifically trained pathologist (S.C.) and senior pathologist (I.Q.)

S.C. and I.Q. read the 32 MSGBs. Interobserver $\kappa$ between S.C. and I.Q. was 0.80 for dFS and 0.93 for dCM. The same slides were read twice by S.C. and the intraobserver $\kappa$ was 1 for dFS and 0.72 for dCM.

Baseline histopathological reports by local pathologists

Table 1 lists the findings described in the reports. Of the 93 baseline local pathology reports, 77 were available for the study; among these, 13 (17%) failed to report the number of foci instead using terms such as many foci or significant number of foci. The CM grade was given in the conclusion in 75 of 77 reports, but 63 of 77 reports gave the FS value. The presence or absence of FLS and NSCS was indicated in only 18.1% and 31.1% of reports, respectively. Germinal centre structures were found in 13 of 89 (14.6%) MSGBs from 10 of 60 (16.6%) patients. The presence or absence of fibrosis was indicated in 35 (45.5%) reports, including 26 describing the presence of fibrosis. The frequent lack of completeness of the local reports may be ascribable to failure of the pathologists to report the absence of features. Acinar depletion was

### Table 1 Intraobserver and interobserver reliability of minor salivary gland biopsy assessment

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intraobserver agreement (centralized reading by S.C.) (n = 89)</th>
<th>Interobserver agreement (baseline local reading vs centralized reading by S.C.) (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\kappa$ (95% CI) Cases, $n$ (%)</td>
<td>Cases with the feature at second reading, $n$ (%)</td>
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<tr>
<td>------------------------------</td>
<td>-------------------------------------------------------------</td>
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<tr>
<td>dFS</td>
<td>1.00 (1.00, 1.00) 89 (100) 47</td>
<td>0.71 (0.62, 0.79) 63 (81.8) 50</td>
</tr>
<tr>
<td>dCM</td>
<td>0.80 (0.73, 0.87) 89 (100) 66</td>
<td>0.64 (0.55, 0.74) 75 (97.4) 50</td>
</tr>
<tr>
<td>Acinar depletion</td>
<td>0.73 (0.66, 0.80) 89 (100) 50</td>
<td>0.41 (0.31, 0.51) 67 (87) 18</td>
</tr>
<tr>
<td>Duct dilatation</td>
<td>0.59 (0.50, 0.68) 89 (100) 32</td>
<td>−0.12 (−0.2, −0.04) 51 (66.2) 3</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.44 (0.35, 0.53) 89 (100) 52</td>
<td>0.16 (−0.01, 0.34) 35 (45.4) 26</td>
</tr>
<tr>
<td>Adiposis</td>
<td>0.53 (0.43, 0.63) 89 (100) 21</td>
<td>1 (1.00, 1.00) 10 (12.9) 2</td>
</tr>
<tr>
<td>FLS</td>
<td>0.71 (0.64, 0.78) 89 (100) 45</td>
<td>0.46 (0.23, 0.70) 14 (18.1) 12</td>
</tr>
<tr>
<td>NSCS</td>
<td>0.64 (0.56, 0.72) 89 (100) 54</td>
<td>0.42 (0.23, 0.69) 24 (31.1) 2</td>
</tr>
<tr>
<td>WLN</td>
<td>0.78 (0.66, 0.90) 89 (100) 8</td>
<td>NS (NS) 3 (3.8) 3</td>
</tr>
<tr>
<td>Confluent foci</td>
<td>0.29 (0.18, 0.40) 89 (100) 8</td>
<td>NS (NS) 3 (3.8) 2</td>
</tr>
<tr>
<td>Germinat centre-like structures</td>
<td>0.67 (0.56, 0.79) 89 (100) 13</td>
<td>NS (NS) 5 (6.4) 5</td>
</tr>
</tbody>
</table>

$\kappa$: dichotomized Chisholm-Mason grade; dFS: dichotomized focus score; FLS: focal lymphocytic sialadenitis; NS: not significant; NSCS: non-specific chronic sialadenitis; WLN: within limits of normal.

S.C. read the 89 MSGBs twice at an interval of 2 months. Table 1 reports the $\kappa$ values, which indicated almost perfect agreement ($\kappa = 1.0$) for dFS and substantial agreement ($\kappa = 0.80$) for dCM. The intraclass correlation coefficient (ICC) for the FS was 0.76 (95% CI 0.66, 0.84) (not shown in Table 1). Agreement was substantial for FLS, NSCS and germinal centre-like structures ($\kappa = 0.71$, $\kappa = 0.64$ and $\kappa = 0.67$, respectively); moderate for fibrosis and duct dilatation ($\kappa = 0.44$ and $\kappa = 0.59$, respectively) and fair for confluent foci ($\kappa = 0.29$).
the most commonly reported feature [67 of 77 (87%)] and was present in 18 of 67 (27%) cases.

**Interobserver agreement**

Interobserver agreement between the local pathologists and S.C. (Table 1) was substantial for dFS and dCM ($\kappa = 0.71$ and $\kappa = 0.64$, respectively). The ICC for FS was 0.66 (95% CI 0.49, 0.78) (not shown in Table 1). Of 63 MSGBs, 55 were concordant for dFS between the local pathologist and S.C. Importantly, the re-evaluation by S.C. led to a change in 8 of 63 (12.6%) diagnoses of the MSGBs. Six (9.5%) MSGBs had FS changed to $<1$ and two (3.1%) to $\geq 1$. Agreement was absent for duct dilatation ($\kappa = -0.12$), slight for fibrosis ($\kappa = 0.16$) and moderate for acinar depletion ($\kappa = 0.41$), FLS ($\kappa = 0.46$) and NSCS ($\kappa = 0.42$). Sample sizes were small, however, for FLS and NSCS and too small for a valid assessment of agreement regarding the other features.

**Difference between CM grade and FS**

The mean number of foci was 3.63 by CM grading and 3 by FS determination, yielding a difference of 0.63. The Bland–Altman plot (Fig. 3) showed systematic bias with overestimation of the number of foci by CM grading. This finding is not surprising, as CM grading takes foci within sites of non-specific chronic sialadenitis into account, thereby inducing a risk of SS overdiagnosis.

**Discussion**

Using data from our previous TEARS study of rituximab in primary SS, we showed here that the reliability for a standardized evaluation of MSGBs from patients with primary SS was substantial. Review by the trained pathologist resulted in a different diagnosis for 12.6% of the patients. MSGB is of prime importance for the diagnosis, classification and prognosis of SS. Validated classification criteria sets for SS incorporate histopathological findings, reflecting the definition of SS as an autoimmune disease involving the exocrine epithelia [30]. However, the methods used to read MSGBs and to write the reports are not standardized. Nevertheless, standardization can be achieved using the detailed protocol described by Daniels et al. [18]. Furthermore, little information is available on the reliability of these new criteria. In keeping with our findings, a 2012 report from Italy indicated that CM grading was still used in most of the seven experienced rheumatology centres [19]. AECG and ACR criteria refer to the method developed by Daniels and Greenspan [6, 7] and specify that the lymphocytic focus count should be performed throughout the normal-appearing mucosa. The CM method does not meet this requirement and consequently cannot be substituted for FS determination. Thus CM grading fails to distinguish between FLS and NSCS. Moreover, CM grading is a categorical scale that does not evaluate severity in patients with FS values $>1$. CM grading overestimates the focus count, as all foci are taken into account.

Reliability may be slightly better for the FS than for CM grading. In the study carried out at seven Italian centres, interobserver agreement for CM grade ranged from 0.44 to 0.92 [19]. A blinded review of the FS in 60 MSGBs from 58 individuals resulted in revision of the initial diagnosis in 53% of cases, although aggregate glandular surface area, gross foci and FS showed high reliability as assessed by regression equations [20]. In another study involving the

**Fig. 3 Bland–Altman assessment of agreement between focus counts by Chisholm–Mason grading and focus score determination**

![Bland-Altman Plot](https://example.com/bland-altman.png)
independent review of 56 MSGBs by two pathologists, agreement was high for the number of foci [ICC 0.97 (95% CI 0.96, 0.99)] and FS [ICC 0.96 (95% CI 0.94, 0.99)] [18]. Discrepancies in focus count can be ascribed to two main factors: a large focus may be counted as several nearly confluent foci or as a single focus and determining whether a lymphocyte aggregate is sufficiently dense to constitute a focus may be challenging. Surface area measurement may be difficult but benefits considerably from the use of an eyepiece graticule or computer-based tools.

Germinall centre–like structures predict severe SS and the development of lymphoma [28]. Their prevalence varied between 18% and 59% in Risselada et al.’s [33] review in which many studies had a FS ≥1 in all MSGBs. Germinall centre–like structures were common in studies in populations with a mean FS >3 or with MALT lymphoma [32, 34, 35]. In this systematic review of 13 cohorts of SS patients, germinall centre–like structures were seen in 25.1% (s.d. 5) of patients [33]. Germinall centre–like structures should be sought routinely, as they may indicate greater disease severity with higher frequencies of lymphadenopathy, leucopenia, hyper-gammaglobulinaemia and extraglandular complications, as well as higher antibody titres [21, 23, 33, 36]. Furthermore, germinall centre–like structures are associated with non-Hodgkin lymphoma [23]. Thus, of seven patients who developed non-Hodgkin lymphoma during 1855 patient-years of follow-up, six had germinall centre–like structures at the diagnosis of primary SS, and the negative predictive value of this feature for lymphoma was high [22].

FLS is the distinctive feature of SS, whereas NSCS is not usually associated with SS [26]. Lymphocytic infiltration of the ductal structures could also be a specific feature of SS and might be a useful criteria [37]. In our study, many local pathologists failed to specify whether FLS and NSCS were present or absent. Challenges may arise when both features are present in the same gland. If FLS predominates, then the FS should be determined. However, it is unclear whether the focus count should include all foci within the gland or only those in FLS areas.

The natural history of minor salivary gland alterations in SS patients remains unclear. Until now, the FS and fibrosis were believed to increase over time and with disease progression [38, 39]. However, in a recent study of serial MSGBs from 28 patients with SS and a median follow-up of 55 months, neither the infiltration grade nor the FS values changed significantly, although significant disease progression occurred [5]. Neither did significant changes develop for germinall centre–like structures, fibrosis or adiposis. This would indicate that SS lesions are slowly progressing alterations. Another study established that FLS was the key histopathological feature in SS and did not usually progress to fibrosis, although patients with chronic sialadenitis were excluded from this work [17]. Nevertheless, fibrosis of NSCS features has been reported in patients meeting AECG or ACR criteria for SS. Significant associations linking stimulated salivary flow to both the FS and fibrosis have been reported, and neither feature varied with the degree of atrophy [40]. The correlations between oral manifestations and histological features remain unclear. Circular reasoning limits the validity of many studies. The identification of sensitive, specific and reliable criteria has become a key objective since the introduction of immunosuppressant therapy for SS. Among responders to the immunosuppressant mizoribine, those with marked lymphocytic infiltration and little atrophy and fibrosis significantly increased their salivary secretion volume in contrast to those with limited lymphocytic infiltration and major atrophy and fibrosis [41]. No other published data are available on the relationships between MSGB features and the response to immunosuppressants in patients with SS [42, 43].

MSGB is a key tool for the diagnosis of SS. In everyday practice, many of the useful histopathological features are underevaluated. Given the major role for MSGB findings in the classification and outcome prediction of patients with SS, standardization is required. Reliability was good in our study for most of the main MSGB features after a training session. Further effort is needed to standardize the evaluation of lymphocytic infiltrates and the FS, particularly for monitoring the response of SS to immunosuppressant therapy.

Acknowledgements

We thank the French rheumatologists and pathologists who referred their patients and biopsies to the TEARS subcohort. We are grateful to Marie Jezequel (Clinical Investigation Centre) for centralizing the biopsies. We thank the staff and particularly the pathology department technicians (Brest Teaching Hospital) for the time and dedication they gave to this study. Rituximab for the TEARS study was donated by Roche (Boulogne Billancourt, France).

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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