Primary Sjögren’s Syndrome
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Chapter 4C

Need for consensus guidelines to standardize the assessment of germinal centers and other histopathological parameters in salivary gland tissue of patients with primary Sjögren’s syndrome

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We have read with great interest the article by van Roon et al. [1] commenting to our paper ‘Towards personalised treatment in primary Sjögren’s syndrome: baseline parotid histopathology predicts responsiveness to rituximab treatment’ [2]. The authors argue that there is a need of standardization of the histopathological characteristics of salivary gland tissue of patients with primary Sjögren’s syndrome (pSS), in general, and of the presence of germinal centers (GCs), in particular.

We fully agree with van Roon et al. and other authors about the need for consensus guidelines to standardize the histopathological evaluation of salivary gland biopsies in pSS patients [1,3]. A standardized scoring system may facilitate prognostication and stratification of pSS patients and is needed for a valid evaluation of various clinical trials [3]. In particular, histological definition of GCs in salivary gland tissue is warranted, since these structures can be difficult to detect in diagnostic hematoxylin & eosin (H&E)-stained tissue sections. Detection of GCs in the periductal lymphoid infiltrates of the salivary glands is clinically relevant, because the presence of these structures is associated with more severe disease [4]. Importantly, the presence of GCs in minor salivary gland biopsies has been postulated to be a predictor of patients who are at risk for lymphoma development [5,6]. It has to be mentioned, however, that recently, we were not able to confirm these findings for a larger number of mucosa associated lymphoid tissue (MALT) lymphomas in parotid glands of pSS patients (Haacke et al., unpublished data).

In our study, we defined GCs in H&E stained sections as lighter areas within the lymphoid infiltrate composed of both lymphoid cells (centrocytes, centroblasts) and of cells with a non-lymphoid nature (macrophages and follicular dendritic cells (FDCs)) (Figure 1A) [1]. Furthermore, the GCs were scored independently by two experienced pathologists. For the inexperienced eye, GCs may be overlooked, because of their small size, or lighter areas within the infiltrate may erroneously be scored as GCs, while in fact they represent lymphoepithelial lesions. For proper and easy detection of GCs, also by less trained persons, additional immunohistochemical staining might be helpful. Therefore, we propose to stain for B-cell lymphoma 6 (Bcl-6) to define and identify GCs. Bcl-6 is a transcription factor expressed at high levels by GC B-cells. Like GCs in peripheral lymphoid organs, GCs in salivary glands of patients with pSS are also consistently positive for Bcl-6 [5]. As shown in Figure 1B, staining for Bcl-6 allows easy and unequivocal detection and scoring of GCs in salivary gland biopsies, both in minor and major (parotid) salivary glands. Implementation of Bcl-6 staining is relatively easy, since it is routinely used in pathology laboratories worldwide for the diagnosis of lymphomas [7]. Other markers, as proposed by Fisher et al. and van Roon et al. [1,3], are less specific and less suitable to detect GCs in routine diagnostics. For example, activation induced deaminase, an enzyme essential for the function of GCs B-cells, is expressed only by a minority of GCs B-cells in minor salivary glands of pSS patients [5], which may make GCs harder to detect. The long isoform of CD21 (CD21L) has also been suggested for detection of GCs. CD21L is expressed by follicular dendritic cells (FDCs). However, although FDCs are a prerequisite for GC function and development, the presence of these cells does not necessarily imply that GCs are present. Indeed, ectopic lymphoid infiltrates in salivary gland tissue of pSS patients can contain FDC-networks in the absence of GCs [8,9]. Staining for the long isoform of CD21 may therefore result in an overestimation of the number of GCs present in salivary gland tissue.

In our study, we observed that a relative high proportion of the parotid salivary gland biopsies presented with GCs at baseline; 67% and 68% of patients in the placebo and rituximab treated group, respectively [2]. These are relatively high percentages compared to the general pSS population, in which approximately one-quarter of the minor salivary gland biopsies exhibit GCs [4]. The reason of this high baseline characteristic can be attributed to the inclusion criteria of our study. In our study the pSS patients were all positive for anti-SSA antibodies and had high systemic activity, as indicated by the relatively high ESSDAI scores [10]. Indeed, presence of GCs in minor salivary glands has been associated with more severe disease, including systemic pro-inflammatory mediators and anti-SSA antibodies [4]. A second explanation for the high number of GCs at baseline might be related to histopathological differences between minor and parotid salivary gland biopsies. Although a previous study in a small cohort of pSS patients (n=30) did not report a difference in numbers of GCs [11], it remains possible that there are more and/or larger GCs in parotid gland biopsies compared to minor salivary glands. Apparently, there is a petition for larger studies focusing on the inherent differences in the histopathological characteristics of parotid and minor salivary gland tissue in both pSS patients and healthy controls.
In summary, in agreement with van Roon et al. [1], we would also like to emphasize that there is a need for consensus guidelines to standardize the evaluation of ectopic lymphoid infiltrates and GCs in salivary gland tissue of pSS patients. The various methods used for automated analysis of several parameters should also be taken into account [12]. Consensus guidelines will assist the pathologist to correctly identify and quantify histopathological parameters in pSS and contribute to a more accurate prediction of disease progression and personalized treatment, as well as allowing the comparison between study cohorts and different clinical trials.

References


Chapter 5

e-Patient education