Towards standardisation of histopathological assessments of germinal centres and lymphoid structures in primary Sjögren's syndrome

We read with great interest the study by Delli *et al*,[1] indicating the potential value of baseline salivary gland histopathology to predict response to rituximab (RTX) therapy. In their study, the authors report that RTX treatment significantly affects local inflammation at different levels, including a decrease in numbers of lymphoepithelial lesions, area of focal infiltrates, numbers of B cells and germinal centres (GCs). Interestingly, the presence of a high number of CD20-expressing B cells in parotid gland biopsy at baseline predicted response to RTX treatment. We agree that these observations may facilitate personalised medicine in patients with primary Sjögren's syndrome (pSS). Importantly, the results from this study emphasise the relevance of detailed analysis of salivary gland biopsy tissue. In this respect, we would argue for joint efforts to standardise measurements of local disease parameters. This is particularly relevant because the inhibition of GC may be of pivotal importance for patients for prevention of lymphoma development.

The absence of GC was previously reported to have a very strong negative predictive value for lymphoma development in patients with pSS.[2] As the absence of a high (at least 3) focus score has similarly high negative predictive value for lymphoma development,[3] the exact contributions of focus score, focus size and GC formation to lymphoma development need to be further clarified. In this study, a striking 67% and 68% of patients in the placebo and RTX group, respectively, presented with GC at baseline. This is much higher than the 25.1% ±5.0% reported in a meta-analysis from 2013.[4] Even in groups of selected patients with high focus scores, GCs were present in only 35.3%±14.8% of patients.[4] Of note is the use of parotid gland biopsy samples in this study, while the meta-analysis refers to minor salivary gland measurements, which may partly explain the difference. As described in the methods section, the authors defined GC as a clearly visible lighter area in a lymphocytic infiltrate. A more exhaustive analysis of these structures by staining for markers of follicular dendritic cells (long isoform of CD21 or CD35), follicular T helper cells (PD-1, Bcl-6, CXCL13, SAP), B cells (CD20, Pax-5), proliferation and functional markers (Ki-67 and activation-induced cytidine deaminase) should be used to properly identify these structures.[5 6] As RTX treatment resulted in a clear decrease in local B cell numbers, it stands to reason that the area of focal infiltrates as well as the number of GCs would also be different between responders and non-responders. The absence of differences in these parameters may be related to the different methods used for analysis of these parameters. There are currently no standardised protocols and guidelines for distinguishing GCs in salivary gland biopsies and only the focus score is used in the classification criteria, while aggregate size and the analysed tissue surface are disregarded. However, the inclusion of these parameters in the outcome measures is already in place in several early-phase clinical trials.[7]

The rheumatologic community should search for guidelines to standardise these important measurements in order to properly dissect the contribution of these parameters to local inflammation, in particular lymphoma development, and effective disease management.

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