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Editorial

Ultrasonography of the Salivary Gland in Primary Sjögren Syndrome: Usefulness to Phenotype the Patients

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Major salivary gland ultrasonography (SGUS) is widely used to diagnose primary Sjögren syndrome (pSS) in a large majority of individuals as well as in specific situations, such as when lymphoma is suspected[1,2,3]. It is a powerful and noninvasive procedure that provides a global image of the parenchymal lesions of the major salivary gland and clearly reflects the effect of the disease on the target tissue[4]. Some different scoring systems exist, all of which are based on parenchymal inhomogeneity of the parotid and submandibular glands. In this issue of *The Journal of Rheumatology*, Mossel, *et al* included consecutive primary Sjögren syndrome (pSS) outpatients in a registry of patients called the RESULT cohort; they described a phenotype associated with an elevated US parenchymal score[5]. Based on the Hocevar scoring system, an elevated US score was associated with more severe disease, higher European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score, higher levels of IgG and rheumatoid factor, and more frequent positive parotid gland biopsy, anti-SSA/SSB antibodies, abnormal unstimulated whole saliva, and ocular staining score than SGUS-negative patients. In contrast, patients with an elevated ultrasound (US) score had less fatigue and pain than those without US lesions.

Despite some bias (longer disease duration in the elevated US score group and the absence of similar results in other cohorts), it is believed that SGUS may help to delineate a specific phenotype of pSS, echoing other results under investigation. Tarn, *et al*[6] described 4 different phenotypes of patients based on patient-reported outcomes and symptoms; within 2 groups, the predominance of fatigue was underlined by different biological processes. This led to an ongoing European project named Stratified Medicine in Primary Sjögren's Syndrome. This also highlights the fact that fatigue seems to be a complex symptom, probably driven by genetics and heterogeneous components. Another project[7] aimed to reclassify systemic autoimmune diseases and to describe different genotypes/phenotypes of patients, including those with SS (PRECISESADS; ClinicalTrials.gov: NCT02890121). Therefore, the SGUS score could be used to define subtypes of patients when combined with clinical symptoms.

Mossel, *et al* also noted the high frequency of SGUS abnormalities in patients with pSS[5]. A total of 79% (136/172) of their patients had parenchymal inhomogeneity, with a mean disease duration of 8.0 (4.0–13.0) years. This highlights the interest in the US procedure in classifying pSS. We and others have also demonstrated that SGUS has high accuracy for diagnosing pSS with a recent disease duration of less than 5 years[8,9]. It is also used in the ACR/EULAR 2016 classification criteria[10]. The addition of SGUS as a minor item increases the sensitivity in the whole cohort from 90.2% to 95.6% according to expert opinions and increases the sensitivity in a cohort of patients suspected of having Sjörgren syndrome from 87% to 93%. Therefore, SGUS has good diagnostic and classification accuracy for pSS.

Finally, in their study, Mossel, *et al* showed that an elevated US score was associated with a longer disease duration[5]. Only 36 patients had a low US score, with a mean disease duration of 5.0 (3.0–8.8) years. However, in the group of patients with abnormal US scores, the disease duration was similar between those with medium (n = 67) and high (n = 69) US scores. This trend suggests that SS progresses slowly, leading to parenchymal destruction. However, this point remains questionable. The question is whether this high score is linked to the duration of the disease or to its overall activity, as stated by the authors. It is difficult in the absence of a real prospective cohort to describe the pathological progression of the parenchyma, and relevant data are lacking; however, we know that scoring SGUS lesions using

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a global score with a 2-year interval did not demonstrate strong evolution of the score[11]. On US, it is believed that anechoic or hypoechoic foci are related to inflammation inside the gland. Fibrosis is defined as the presence of hyperechoic bands in fibrotic tissue indistinguishable from adjacent tissue. Another stage related to terminal modification of the parenchyma is the presence of fatty lesions that are homogeneously hyperechoic. However, we still need to explore the biopathological process leading to irreversible lesions, as well as the close relationship between inflammation and fibrosis inside the parenchyma. More recent therapeutic trials have demonstrated that we can interfere with the parenchymal process, and the results of SGUS suggest for the first time that in some cases, the parenchyma can be partially restored by immunotherapy[12,13].

Therefore, SGUS is a simple and very informative procedure that is not only helpful at the patient level for the diagnosis and classification of SS but also serves as a window for an autoimmunity target that can be combined with other data to delineate the phenotypes of patients and endpoints for clinical trials.

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