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Shear wave elastography as a new method to identify parotid lymphoma in primary Sjögren Syndrome patients: an observational study

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Abstract

Parotid non-Hodgkin lymphoma (NHL) in primary Sjögren syndrome (pSS) has no specific biomarker for diagnosis. Salivary glands ultrasound (US) is largely used, but its contribution in detecting parotid NHL has not been established. The aim of our study was to determine the added value of bidimensional shear wave elastography (2D-SWE) in pSS diagnosis and to determine its accuracy in identifying parotid NHL. Grey-scale US (GSUS) and 2D-SWE of salivary glands were performed in 35 patients with pSS and 35 healthy controls. The GSUS scores were calculated and the mean of three SWE consecutive measurements was used to appreciate the gland stiffness. SWE increase the diagnostic rate at a cut-off of 6.45 kPa (from 88.6 to 94.2%, $p < 0.001$) only if applied in patients with insufficient GSUS criteria for pSS diagnosis. The parotid glands with NHL (8 patients, all mucosa-associated lymphoid tissue type) had hyperechoic bands in more than half of the glandular parenchyma (in 68.75% of the glands), large hypoechoic area > 20 mm (all glands), traced gland area over 5 cm^2 (all glands), parotid US score greater than 13 (in 68.75% of the glands), and high stiffness (elasticity modulus 13.9 ± 4.08 vs 6.32 ± 2.24) (all $p < 0.001$). These findings give high sensitivity (92.3%), specificity (100%), and positive (100%) and negative predictive values (98.3%) for NHL identification. The rest of GSUS findings did not correlate with the classic risk factors for lymphoma development (all $p > 0.05$). 2D-SWE had added value for pSS diagnosis in cases where GSUS aspect is normal or nonspecific. The higher stiffness of parotid NHL can be used for early diagnosis, biopsy guidance, and, possible, for treatment monitoring.

Keywords Ultrasonography · Shear wave elastography · Primary Sjögren's syndrome · Parotid lymphoma

Introduction

Primary Sjögren syndrome (pSS) has an increased risk for developing non-Hodgkin's lymphoma (NHL) [1] which is a cause of mortality in pSS patients. Clinical and biological

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predictor factors for lymphoma transformation were largely studied [2–4], but despite the obtained results, the biopsy remains mandatory for a positive diagnosis.

Ultrasonography (US) is considered an excellent tool in guiding biopsy, but the US findings for lymphoma transformation in pSS patients are not specific [5] and due to the diffuse modification of the glands, the early identification of the lesion is not always possible. Magnetic resonance imaging (MRI) is the imaging techniques with the best results in differentiating malignant from benign parotid lesions [6–9], but data about NHL in pSS are scarce. During time, several US scoring systems were developed to improve diagnostic sensitivity and specificity of the method [10–12]. Recently, consensual definitions of US findings in normal and pSS salivary glands were published and the inter- and intra-observer reliability of the US evaluation was assessed [13], but currently, the diagnosis of pSS is based on the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria [14] in which no US criteria are included.

The principle of US elastography relies on measuring the internal tissue shear deformations which results after quasi-static or dynamic forces are applied [15]. Using strain and acoustic radiation force impulse elastography, the salivary glands parenchyma proved to be stiffer in pSS patients [16–19]. Bidimensional share wave elastography (2D-SWE) is a new user-independent elastographic technique in which tissue elasticity is measured by the real-time guidance of B-mode image, creating a color-coded image where, using a region of interest (ROI) box, the elasticity of the explored tissue is measured. The elasticity is expressed as elasticity modulus/estimated tissue stiffness (or Young's modulus), measured in kiloPascals (kPa) or as shear wave velocity (m/s) [15]. The method was largely accepted for hepatic and non-hepatic pathology [15, 20], including tumoral parotid lesions [6, 21], demonstrating higher stiffness of malignant tumors, but few data are available in pSS patients [22, 23]. Recently, our group published the normal values of salivary glands stiffness using 2D-SWE in healthy population [24].

Therefore, the purpose of our work was to assess the salivary glands stiffness using 2D-SWE technique in pSS patients and to evaluate its added value for diagnosis and, especially, for parotid NHL complication.

Methods

Patients

Fifty-one patients with Sjögren syndrome (SS) were included in this observational, cross-sectional study, conducted between June and July 2018 in our department. The diagnosis of pSS was established based on ACR/EULAR classification criteria [14]. Patients with secondary SS (9), hepatic virus C infection (3), sialolithiasis (3), and previous radiation of the neck region (1) were excluded. We selected 35 healthy subjects from the medical staff with no prior pathology related to the salivary glands matched for age, sex, and body mass index (BMI) as the control group. The study was approved by the Ethics Committee of the University and each subject signed informed consent before enrolling.

Clinical evaluation

The demographic and disease history data were collected and clinical examination was performed. A 0–2 grading scale questionnaire regarding the severity of xerostomia and xeroftalmia during the last 2 weeks (0—without symptoms, 1—mild symptoms with symptomatic treatment, 2—severe symptoms even with symptomatic treatment) was completed by every pSS patient. The EULAR Sjögren's syndrome disease activity index (ESSDAI) was calculated [25]; Schirmer test in 5 min (mm) and unstimulated whole salivary flow (UWSF) at 15 min (ml) were performed. The classical predictors for NHL were evaluated [3]. All the clinical tests and data collections were performed by a rheumatologist with 5 year experience, blinded to US examination.

Grey-scale US and 2D-SWE examination

US evaluation was performed using Supersonic Imagine AixplorerUltimate (SuperSonic Imagine, Aix-en-Provence, France, with SuperSonic Imagine's UltraFast™ software technology) machine with multi-frequency linear transducer (SL18-5 MHz), following the published recommendation [15, 26].

The examination started with grey-scale US (GSUS) and the analyzed parameters were according to Jousse-Joulin et al. [26] 7 core items: (1) echogenicity (normal/abnormal); (2) homogeneity (normal/abnormal); (3) hyperechoic bands (none, $<50\%$, and $>50\%$ of the parenchyma); (4) hypoechoic areas [number (0, 1–4, and ≥ 5), location (none, isolated, localized, scattered and diffuse), and size (mm)]; (5) normal and pathologic lymph nodes (yes/no); (6) calcifications (yes/no); and (7) posterior border visibility (yes/no). Bilateral parotid (0–32, 0–16 for one gland), submandibular (0–32, 0–16 for one gland), and total (parotid and submandibular, 0–64) US scores have been calculated following the scores previously established [26]. The measured surface area was achieved by drawing the area on the screen machine and adjusting the US focus for deep structures.

The examination continued with 2D-SWE, using the elasticity modulus (Young's modulus E). After obtaining a proper color-coded image, three consecutive measurements using a 3 mm diameter Q-box were realized and the mean was used for further analysis. The box was placed in

a highly modified parenchyma, in a region free of vessels, cystic transformation or fibrosis, between 1 and 2 cm from the anterior glandular contour. We considered the vertical striped artifact and all measurements were performed between the artifactual stripes (Fig. 1).

The US images were stocked and retrospectively analyzed by two examiners, blinded to each other's and the subjects examined. Both examiners completed a standardized worksheet and, finally, concluded if the GSUS aspect is suggestive for pSS diagnosis. The disagreements were reviewed together with a third examiner with more than 20 years of experience in salivary glands US.

Statistical analysis

Shapiro–Wilk test was used to assess normal distribution. The data were presented as mean ± standard deviation (SD) for normally distributed continuous variables or median (interquartile range) for non-normally distributed continuous variables and percentages for categorical variables. Chi-square or Fisher's exact tests were used to assess the association between categorical variables. Spearman's rank correlation coefficient was calculated to assess the correlation between ordinal variables. The differences of the means or medians were evaluated using the independent-samples *T* test for normally distributed continuous variables, and Mann–Whitney *U* test (2 samples) and Kruskal–Wallis one-way ANOVA (> 2 samples) for non-normally distributed continuous variables, respectively. The inter-observer agreement for the US parameters (dichotomous or ordinal variables) was assessed using Cohen's kappa and weighted Cohen's kappa, respectively. *P* value < 0.05 was considered statistically significant.

The diagnostic performance of the tests was analyzed using Receiver-Operating Characteristic (ROC) analysis and the area under the ROC curve (AUC). The discriminant cut-off points were chosen depending on the highest sensitivity (Se) and specificity (Sp). The positive and negative predictive values (PPV, NPV) for these tests were also calculated. IMB SPSS Statistics v.23 and Microsoft Office 365 Excel were used.

Results

Descriptive data of patients with pSS are presented in Table 1 and the GSUS findings together with interobserver agreement for the analyzed items are detailed in Online Resource 1. The positive diagnosis of pSS in GSUS had good inter-observer agreement ($k = 0.75$).

We established an optimal cut-off value of 5 for parotid and submandibular US score and 10 for total US score (Se 88.6% and Sp 100% for GSUS in pSS identification). 2D-SWE threshold for pSS prediction was established at 6.45 kPa (Se 58.6%, Sp 80%). Appling this value in pSS patients with normal/ambiguous GSUS finding, the

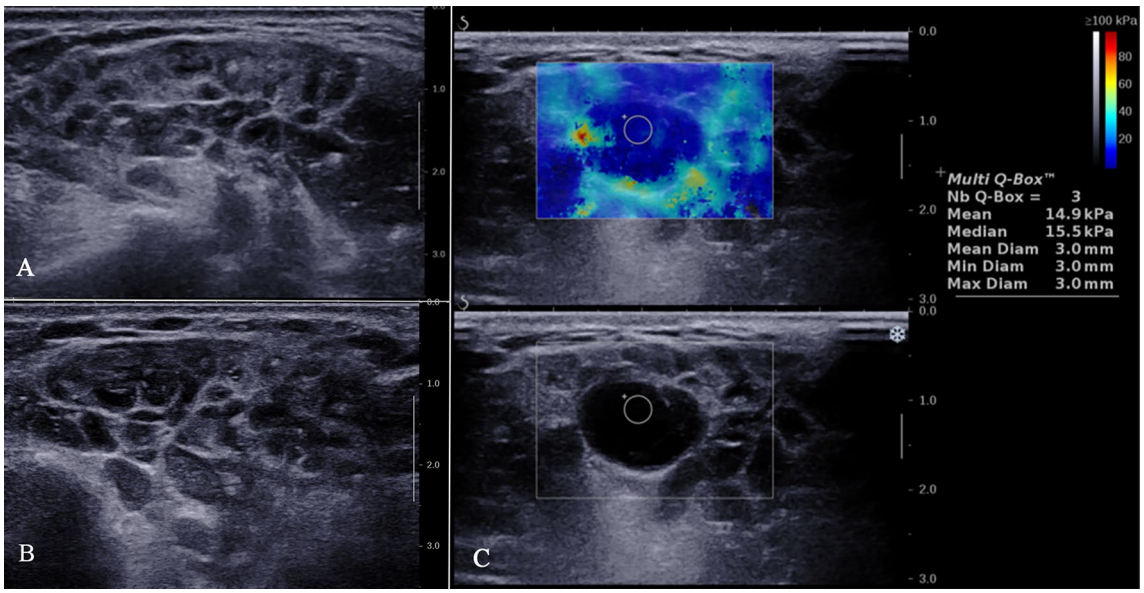

Fig. 1 Parotid gland ultrasound modification in a patient with Sjögren syndrome and parotid lymphoma complication. In longitudinal (**a**) and transverse (**b**) ultrasound of parotid gland severe changes are present: diffuse inhomogeneity with hypoechoic areas in the entire gland and hyperechoic bands. **c** Shear wave ultrasound (top, color-coded imagine with placement of the Q-box and bottom, the corresponding grey-scale US imagine). In the left, the obtained values after three measurements, showing high elasticity modulus (high stiffness) suggesting parotid lymphoma

Table 1 Descriptive data of the primary Sjögren syndrome patients

Variable ($n=35$)	
Age (years)	57.09 ± 12.14
Female:male	33:2
BMI (kg/m^2)	25.84 ± 4.52
Dry eyes	94.3
Dry mouth	94.3
Schirmer's test (mm)	2 ± 0.61
UWSF (ml)	1.2 ± 0.32
Anti-SSA autoantibodies	80
Anti-SSB autoantibodies	42.9
Rheumatoid factor	71.4
Positive biopsy	65.7
Disease duration (months)	34(13–60)
Extraglandular manifestation	
Arthralgia and/or arthritis	60
Fatigability	31.4
Treatment	
Hydroxychloroquine	88.6
Methotrexate	25.7
Artificial tears	88.6
Pilocarpine	11.4

The results are expressed as mean ± standard deviation (SD), percent (%), or median (interquartile range)

n number of patients, *BMI* body mass index, *UWSF* unstimulated whole salivary flow

correctness of US positive diagnosis increased at 94.28% (Table 2).

A low negative statistical correlation ($r=-0.314$) between GSUS total score and UWSF was found ($p<0.05$), but no correlation with disease duration or ESSDAI was established (all $p>0.05$).

Higher values of the elasticity index were obtained in pSS group only in parotid glands compared to healthy subjects (8.05 ± 4.21 kPa vs 5.39 ± 1.45 kPa in parotid gland, $p<0.001$ and 8.19 ± 3.47 kPa vs 8.53 ± 1.89 kPa in submandibular gland, $p=0.153$). The difference was especially related to the presence of NHL in the parotid gland in eight patients (female/male = 7/1, mean age 51.88 ± 15.4 years, mean BMI 28.46 ± 5.62 kg/m^2), histologically all mucosa-associated lymphoid tissue (MALT) type (details about the NHL diagnosis process not shown here). All patients with pSS and NHL had disease-modifying antirheumatic drugs (DMARDs) treatment (62.5% Hydroxycloroquine, 12.5% Methotrexate, and 25% Hydroxycloroquine and Methotrexate). No patients (with or without NHL) had glucocorticosteroids in treatment at the moment when they were included in the study. Elasticity index was higher in NHL area comparing with non-NHL glands (13.9 ± 4.08 kPa vs 6.32 ± 2.24 kPa, $p<0.001$). The parotid gland with lymphoma had hyperechoic bands in more than half of the glandular parenchyma (in 68.75% of the glands), large hypoechoic area > 20 mm (all glands), gland area over 5 cm^2, and parotid US score greater than 13 (in 68.75% of the glands) (all $p<0.001$). The rest of GSUS parameters did not correlate with the risk factors for lymphoma development found in these patients (all $p>0.05$). The cut-off values for the parotid US score and 2D-SWE (13 and 11.2 kPa, respectively) were calculated to predict the NHL complication in pSS patients (Table 2).

Parotid gland enlargement (from slight to significant) and the positive results of the anti Ro and/or anti La antibody and rheumatoid factor (RF) were the most frequent risk factors in our NHL group (Table 3). Most of the predictive risk factors had a positive association with the parotid US score and 2D-SWE (Table 3). Disease duration did not correlate with the development of NHL complication [a median of 31.5 months (13.0–66.0), $p>0.05$].

Based on our GSUS and 2D-SWE findings, we developed in Fig. 2 a diagnosis algorithm for the pSS patients and those with the suspicion of parotid lymphoma transformation.

The presence of hypoechoic area larger than 20 mm with elasticity index over 11.2 kPa in a clinical swollen parotid gland with US traced area of parotid gland more than 5 cm^2, typical GSUS aspect of pSS, hyperechoic

Table 2 Performance of parotid and submandibular ultrasound score and elasticity modulus in pSS patients compared with healthy subjects and in pSS patients with and without parotid lymphoma complication

	Cut-off	AUC	Se (%)	Sp (%)	*p* value	PPV (%)	NPV (%)
Healthy subjects versus pSS							
Total US score (0–64)	10	0.956	88.6	100	< 0.001	100	89.7
Parotid US score (0–32)	5	0.94	88.6	100	< 0.001	100	89.7
Submandibular US score (0–32)	5	0.959	88.6	100	< 0.001	100	89.7
SWE parotid gland (kPa)	6.45	0.709	58.6	80	< 0.001	73.6	64.4
pSS without lymphoma versus pSS with parotid lymphoma development							
Parotid US score (0–16)	13	0.951	84.6	100	< 0.001	96.6	100
SWE parotid gland (kPa)	11.2	0.994	92.3	99.9	< 0.001	98.2	92.3

pSS primary Sjögren syndrome, *SWE* shear wave elastography, *kPa* kilopascals, *US* ultrasound, *Se* sensitivity, *Sp* specificity, *AUC* area under curve, *PPN* positive predictive values, *NPV* negative predictive values

Table 3 Presence of clinical and biological risk factors for non-Hodgkin lymphoma development in primary Sjögren syndrome patients and the association between these factors and the positive NHL diagnosis, parotid US score, and 2D-SWE

	The presence of risk factors (%) $n = 8$	p value for the association with positive NHL diagnosis	p value for the association with parotid US score (cut-off > 13)	p value for the association with 2D-SWE (cut-off > 11.2 kPa)
Clinical factors				
Parotid gland enlargement	100	< 0.001	< 0.001	< 0.001
Palpable purpura	12	< 0.05	< 0.05	< 0.05
Raynaud's phenomenon	0	*	*	*
PNS involvement	12	0.62	0.24	0.322
Lymphadenopathy	0	*	*	*
Splenomegaly	0	*	*	*
Biological factors				
Lymphopenia	50	0.068	0.088	0.094
Anemia	0	0.567	> 0.99	> 0.99
Monoclonal gammopathy	25	< 0.05	< 0.05	< 0.05
Anti Ro and/or anti La positivity	100	0.055	0.191	0.105
RF positivity	100	< 0.05	< 0.05	< 0.05
Cryoglobulinemia	12	< 0.05	< 0.05	< 0.05
Low C4 levels	50	< 0.001	< 0.001	< 0.001
Higher minor salivary gland biopsy focus score	NA	*	*	*

The results are expressed as percent

pSS primary Sjögren syndrome, *n* number of patients, *PNS* peripheral nervous system, *RF* rheumatoid factor, *C4* complement C4, *NA* not applicable, *NHL* non-Hodgkin lymphoma, *US* ultrasound, *2D-SWE* two-dimensional share wave elastography

*Statistics not available (constant variable)

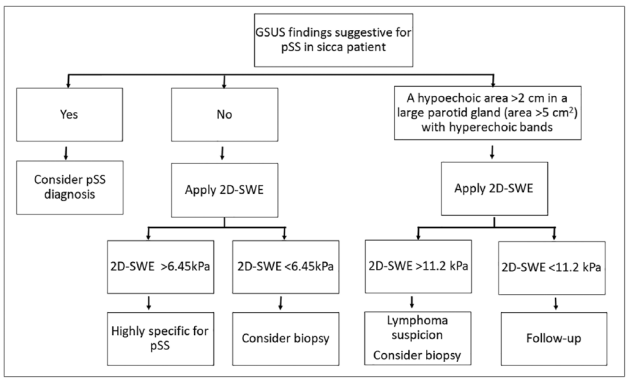

Fig. 2 Algorithm for the pSS diagnosis and non-Hodgkin lymphoma (NHL) complication using grey scale ultrasound (GSUS) and two-dimensional share wave elastography (2D-SWE) in salivary glands

bands in more than half of the glandular parenchyma and an US parotid score greater than 13, raised the suspicion of MALT lymphoma with 92.3% Se, 100% Sp, 100% PPV, and 98.3% NPV.

Discussion

In this study, we showed that, in patients with insufficient criteria in GSUS for pSS diagnosis, SWE increased the diagnostic rate at a cut-off value of 6.45 kPa. These results cannot be compared with the results obtained by Arslan et al. [23] as the authors used a different machine (Toshiba Aplio 500) and the elasticity modulus was calculated as shear wave velocity (m/s) for the parotid gland.

The main application of 2D-SWE was found for parotid MALT lymphoma identification, a cut-off value of 11.2 kPa in elasticity index giving an excellent Se and Sp for diagnosis. According to our knowledge, no data about SWE in parotid lymphoma of pSS patients were published.

Bhatia et al. [21] applied SWE in parotid tumors, but they had only one case with NHL (13.5 kPa). The author demonstrated that no parotid focal lesion had uniform elastic modulus and, for this reason, we realized three measurements in different parts of the hypoechoic area. High stiffness was also found in cervical lymph-node lymphoma in adults and children [27, 28], showing that SWE provided diagnostic accuracy in determining the type of pathology.

The malignant tumors become stiffer while growing in the host tissue due to the proliferation of cancer cells

and extracellular matrix components [29]. For this reason, SWE can be considered as imaging biomarker for MALT lymphoma in pSS patients.

The presence of previous studied risk factors in pSS patients [2–4] is important for the early diagnosis of the NHL complication. In our NHL group, the parotid US score and 2D-SWE correlated to the most frequent prognostic risk factors described by Retamozo el al [30]. We suggest that these imaging methods, and especially 2D-SWE, could be used in the parotid lymphoma detection together with the actual clinical, biological, and histopathological risk factors. Our algorithm for using GSUS and 2D-SWE in salivary glands can be easily applied in daily practice and help clinicians to better diagnosis pSS patients and parotid NHL complication.

Our study has some limitations. First, the small number of pSS patients with NHL. This is related to the short period of time of the study and the monocentric design. SuperSonic machines are new and expensive equipments and rarely found in Rheumatology Departments, making a multicentre study with homogeneous results unattainable. As in our group, all the patients had MALT lymphoma, we cannot generalize the conclusion for other NHL types. It would have been useful to compare our US results with the lymphocytic focus score of the NHL group, but it was available only in a few cases. Due to ethical considerations, the re-biopsy was considered as an invasive method.

In conclusion, the added value of SWE technique was relevant for US pSS diagnosis in cases where the GSUS findings were normal or nonspecific, but the higher stiffness of MALT lymphoma can be used for early diagnosis, biopsy guidance, and, possible, for treatment monitoring. 2D-SWE of the parotid glands should be considered as a promising imaging technique for detection of parotid lymphoma complication in pSS patients. Larger studies are needed to establish the cut-off values on different equipments and to validate these preliminary results.

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Author contributions Conception and design of the study: MB, OS, DF. Data collection, acquisition, analysis, and interpretation of data for the study: MB OS, LM, CB, MM, DF. Statistical analysis: OS. Drafting the work and manuscript preparation: MB, LD, IF, DF. Manuscript revision: LD, OS, MM, DF. All authors approved the final version of manuscript.

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Compliance with ethical statement

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All patients gave written informed consent in accordance with the declaration of Helsinki. Approval was obtained from the ethics committee of University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca (Date of approval: 2 April 2018/No. of approval 166).

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