Sonographic features of lymphoma of the major salivary glands diagnosed with ultrasound-guided core needle biopsy in Sjögren's syndrome

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ABSTRACT

Objective. *To identify ultrasound (US) features of lymphomas (L) of major salivary glands (SGs) in primary Sjögren's syndrome (pSS) patients and to differentiate US pattern of L and non-L.*

Methods. *Prospectively, from September 2019 to March 2021, 27 pSS-patients with clinical findings suspicious for L of the SGs underwent US evaluation followed by US-guided core-needle biopsy (CNB). For each patient, we assessed the OMERACT score, dichotomised (0/1 "lower", 2/3 "higher"), and we compared it between L-pSS and nonL-pSS groups. For focal lesions, echogenicity, inner appearance, shape, margins, presence of septa, vascularisation and posterior acoustic features were also assessed and compared between the two groups; we planned to consider as "suspicious" features more frequently associated with L. We expected to compare frequencies at which two or more "suspicious" features were simultaneously present between L-pSS and nonL-pSS. p<0.05 were considered statistically significant.*

Results. *L-pSS showed more inhomogeneous glandular pattern (100% vs. 69.2% higher OMERACT; p=0.0407). For focal lesions, the "suspicious" features identified were: OMERACT grade 3, very hypoechoic, homogenous, oval shape, well-defined margins, presence of septa, colour-Doppler vascularisation, posterior acoustic enhancement. 6/8 and 7/8 simultaneous suspicious features were significantly higher among L-pSS patients, compared to nonL-pSS (88.9% vs. 28.6%, p=0.034 for 6/8 features; 77.8% vs. 14.3%, p=0.040 for 7/8 features).*

Conclusions. *L of the major SGs in pSS was always associated with OMERACT scores 2 or 3 and presented with diffuse or focal patterns. For focal lesions, the association of more "suspicious" features made the diagnosis of L increasingly more likely. This information can help to improve planning of US-guided CNB.*

Introduction

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease (1-3), which predominantly involves lacrimal and salivary glands (SGs), with chronic inflammatory infiltration (4, 5). The histologic involvement of the SGs is considered in old and recent classification criteria and has an imaging correlate by different techniques, including salivary gland ultrasound (SGUS) (6, 7).

Patients affected by pSS have an increased risk of developing an extranodal lymphoma of the major SGs, with the usual histotype being a low-grade B-cell non-Hodgkin's lymphoma (NHL) of the mucosa-associated lymphoid tissue type (MALT) (8, 9). It has been recently reported that the B-cell lymphomas occur in 5% of pSS patients, and that parotid swelling is a crucial clinical NHL predictor (10-14).

In patients with suspected or already diagnosed pSS, among imaging techniques, SGUS is a very useful tool, since it is a non-invasive, accessible tool with good sensitivity and specificity for echostructural abnormalities of the parotid and submandibular glands (6,15). Recently, SGUS proved to be useful to improve the diagnostic performance of both American European Consensus Group (AECG) (16) and American College of Rheumatology (ACR) criteria (6). Moreover, SGUS might play a role in monitoring pSS patients in the follow-up (6, 17, 18).

US-guided Core-Needle Biopsy (CNB)

of the major SGs in pSS patients has been proven to be a feasible and effective tool in providing viable tissue samples for pathological examination (4,19). US-guided CNB appears safer than open surgery (which up to now is considered the standard approach to biopsy major SGs) and allows sampling of focal areas within major SGs of pSS patients. This last possibility given by US-guided CNB is of particular interest because lymphoma of the major SGs often presents as a localised lesion (20, 21).

To the best of our knowledge, in pSS patients, sonographic features of lymphoma of major SGs and imaging features that differentiate lymphoma from other conditions of the major SGs have never been reported previously. One might hypothesise that SGs lymphoma in pSS could show distinctive SGUS patterns, helping to differentiate it from other conditions, to guide biopsy and to investigate more biologically relevant tissue areas.

Thus, if confirmed, this possibility could be highly relevant, since the distinction between low-grade malignant and non-malignant lymphoproliferative lesions can be difficult even after biopsy in pSS (22), and the exact site of glandular biopsy may in part explain these difficulties. Furthermore, non-malignant lesions such as myoepithelial sialadenitis (MESA) – with or without clonal B-cell expansion – may be present concomitantly with low grade MALT NHL (22), and sampling of the most suspicious areas could reduce interpretative troubles.

Therefore, the purpose of our study is to identify the sonographic features suspicious for lymphoma (the usual histotype being a B-cell low-grade MALT lymphoma) of the major SGs in pSS patients with salivary gland enlargement, and to investigate which sonographic features could differentiate lymphomas from other conditions in the same clinical setting.

Materials and methods

Patients

This prospective study was approved by the referring Institutional review board of the University of Udine, Italy. Written informed consent was obtained from each patient in accordance with the Declaration of Helsinki and with local guidelines for good clinical practice. From September 2019 to March 2021, twenty-seven consecutive unselected patients with pSS (2016 ACR-EULAR classification criteria (7)) and with clinical findings suspicious for parotid or submandibular lymphoma (due to parotid or submandibular persistent enlargement) were referred to our Institute to undergo a SGUS evaluation followed by US-guided CNB. All these patients were included in our study.

Demographic, clinical and laboratory data

Patients' clinical data were collected from medical charts. The data included age, gender, disease duration, unstimulated sialometry and Schirmer's tests and evidence of serum antibodies, such as antinuclear, anti-Ro/SSA and anti-La/SSB antibodies. Furthermore, the presence of risk factors for lymphoma development in pSS patients was noted at the time of biopsy procedures (glandular swelling, lymphadenopathy, cryoglobulinaemia, a serum monoclonal component, rheumatoid factor, low serum C4 and leukopenia) (12). Finally, we registered all the adverse events of US-guided CNB procedures.

Ultrasound examination and US-guided CNB

Both the US examination and the CNB were performed by one radiologist with 10 years of experience in SGUS and US-guided CNB of superficial lesions, using an Affiniti 70 system (Philips, Eindhoven, the Netherlands) equipped with a linear high-frequency transducer (L18-5 MHz) in a non-operating room. US examination was focused on major SGs, and was performed in the supine position, with a slight hyperextension of the neck. Images and cine-loops were digitally archived (SuiteEstensa release 2.0, v 33.6.3.1, EBIT – Esaote Group, Genoa, Italy).

For biopsies, patients were asked to lie down in the supine position, with shoulders slightly lifted (*i.e.* with a pillow below the upper back) and the neck hyperextended, turned towards the direction opposite to the side in which sampling was planned. After accurate disinfection of the skin and the US probe, under US guidance, a local anaesthetic (5 mL of mepivacaine chlorhydrate) was injected with a fine needle (23 G) in the subcutaneous tissue and in the major SG. For parotid glands, an access from the posterior, caudal part of the gland was preferred, to minimise the chance of facial nerve damage ("safety zone") (23). After a few minutes, a small skin incision was done with a scalpel and, through this incision, always under US guidance, a 14 G semi-automatic needle (Precisa 14G, HS Hospital Service, Aprilia, Italy) was inserted, following the same route used for local anaesthesia. When no focal lesion was present, sampling was performed in the safest possible way (in the "safety zone" in parotid glands), with a sampling length usually set on 20 mm. Obviously, also in cases of focal lesions the safest approach was used; in parotid glands, specifically, to minimise the chance of facial nerve damage, a posterior access from the "safety zone" was used, and the route that ensured the shortest approach was preferred. Two to three samples were obtained per patient (24).

Image analysis

The radiologist that performed SGUS assessed the sonographic features of the SGs according to the OMERACT scoring system (25). The more enlarged gland was reported.

When focal areas were present, their sonographic features were assessed as follows: 1) echogenicity (very hypo-/hypo-/iso-/hyper-echoic), 2) inner appearance (homogeneous/inhomogeneous), 3) shape (oval/round/lobulated), 4) margins (well-defined or ill-defined), 5) presence of septa (present or absent), 6) vascularisation (present or absent at colour-Doppler assessment), 7) posterior acoustic features (posterior enhancement/posterior shadowing/none).

Statistical analysis

Based on the results, we expected to identify two groups, namely the L-pSS group (lymphoma group, which was expected to be mainly represented by low-grade B-cell NHL of MALT) and

Table I. Patients' demographics and characteristics.

Patients' clinical and laboratory features	
Patients, N	27
Gender, female, n (%)	24 (88.9%)
Age at evaluation, mean (SD), years	59.3 years (SD 13.2 years)
Disease duration, mean (SD), years	13.39 years (SD 15.2 years)
Parotid gland enlargement, n/N (%)	20/27 (74.07%)
Submandibular gland enlargement, n/N (%)	7/27 (25.93%)
Anti-Ro/SSA or anti-La/SSB positive, n/N (%)	21/27 (77.78%)
Lymphadenopathy, n/N (%)	11/27 (40.74%)
Cryoglobulinemia, n/N (%)	5/27 (18.51%)
Cryoglobulinaemic vasculitis, n/N (%)	4/27(14.81%)
Serum monoclonal component, n/N (%)	12/27 (44.44%)
Rheumatoid factor positive, n/N (%)	19/27 (70.37%)
Leukopenia (WBC < 4,000/mm3), n/N (%)	8/27 (29.62%)
Low C4, n/N (%)	12/27 (44.44%)

the nonL-pSS group (non-lymphoma group), depending on final pathologic diagnosis.

The OMERACT score and, for focal lesions, the frequencies of each sonographic feature (as reported above) were planned to be assessed and compared between L-pSS and nonL-pSS patients.

With respect to OMERACT score, it was dichotomised in two categories, respectively the "lower OMERACT" score group, which included patients with an OMERACT score of 0 and 1, and the "higher OMERACT" score group, which included patients with an OMERACT score of 2 and 3.

For focal lesions, for each US feature we planned to identify the one most frequently associated with lymphoma. Therefore, we expected to find eight US features (one for each of the seven parameters described above, plus the OMERACT score of the gland in which the lesion was found) associated with lymphoma, and to define them as "suspicious". Then, we planned to report the frequencies at which two or more (up to eight) of these "suspicious" features were simultaneously present, and to compare those frequencies for L-pSS and nonL-pSS groups.

Chi-square and Fisher's exact tests were used to assess statistically significant differences. *p*-values <0.05 were considered statistically significant. Analysis was performed with a commercially available software (MedCalc Software bvba v. 18.11.6, Ostend, Belgium).

Results

Patients' demographic characteristics and laboratory findings

Twenty-seven patients who underwent

Table II. nonL-pSS group. OMERACT Score, sonographic features of focal lesions, when present, and final diagnosis are reported for each of the thirteen patients included.

Patient	OMERACT score	Diagnosis (Pathology)	Focal Lesion	Echostructure (FL)	Inner Appearance (FL)	Shape (FL)	Margins (FL)	Presence of Septa (FL)	Hyper-vascular (FL)	Posterior Acoustic Features (FL)
#1	2	Reactive lymph node	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	No	No	Posterior enhancement
#2	2	Myoepithelial sialadenitis	Yes	Very Hypoechoic	Homogeneous	Lobulated	Well-defined	Yes	Yes	Posterior enhancement
#3	2	Sarcoidosis	No	-	-	-	-	-	-	-
#4	2	Chronic inflammation with lymphoplasmacytic infiltration	Yes	Hypoechoic	Homogeneous	Oval	Well-defined	No	No	None
#5	1	Chronic inflammation with lymphoplasmacytic infiltration	Yes	Hypoechoic	Homogeneous	Lobulated	Well-defined	Yes	No	Posterior enhancement
#6	1	Myoepithelial sialadenitis	No	-	-	-	-	-	-	-
#7	3	IgG4-related disease	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	No	Yes	Posterior enhancement
#8	3	Chronic sialadenitis	No	-	-	-	-	-	-	-
#9	1	Chronic sialadenitis	Yes	Hyperechoic	Inhomogeneous	Lobulated	Ill-defined	No	No	Posterior shadowing
#10	3	Myoepithelial sialadenitis	No	-	-	-	-	-	-	-
#11	3	Non-neoplastic B-cell lymphoproliferation	Yes	Hypoechoic	Inhomogeneous	Oval	Well-defined	No	Yes	Posterior enhancement
#12	3	Epithelial hyperplasia with features ambiguous for lymphoma	No	-	-	-	-	-	-	-
#13	1	Myoepithelial sialadenitis	No	-	-	-	-	-	-	-

US-guided CNB of the parotid or submandibular glands were evaluated. Of these patients, 24 (88.9%) were females and 3 (11.1%) were males. Patients' mean age at the time of the biopsies was 59.3 years (Standard Deviation [SD] 13.3 years). All patients presented parotid or submandibular swelling. 21 patients presented anti Ro/SSA antibodies, whilst 10 presented anti La/SSB antibodies. Patients' clinical characteristics are shown in Table I. Enough viable tissue for pathological evaluation was obtained in all cases through CNB. Transient adverse effects after CNB occurred in four patients (three cases of transitory facial nerve paralysis and one case of oral bleeding): all of them regressed after a short observation period, without need of further intervention.

Lymphoma was histologically confirmed in 14 cases (51.9%), and always proved to be a low-grade B-cell NHL of MALT. Of the 13 (48.1%) remaining patients, a definite pathological diagnosis different from lymphoma was achieved in all cases. The pathological diagnoses of the non-NHL conditions are summarised in Table II.

The frequencies of OMERACT scores and of the sonographic features of focal lesions (when present) are reported and summarised in Table III, for both L-pSS and nonL-pSS. A more detailed analysis is reported below.

OMERACT SGUS score

Overall, salivary lymphomas showed a more inhomogeneous glandular pattern (100% *vs*. 69.2% higher OMERACT; p=0.0407). Furthermore, L-pSS patients never presented a low (0 or 1) OMERACT score.

Specifically, L-pSS patients were 0/14 (0%) grade 0, 0/14 (0%) grade 1, 4/14 (28.6%) grade 2 and 10/14 (71.4%) grade 3, according to the OMERACT scoring system (25). Therefore, all (100%) the major SGs of the L-pSS group were part of the "higher OMERACT", as described above.

By contrast, nonL-pSS patients were assessed respectively as grade 0 in 0/13 (0%), grade 1 in 4/13 (30.8%), grade 2 in 4/13 (30.8%), and grade 3 in 5/13 (38.4%). Therefore, 9/13 (69.2%) of the major SGs in the nonL-pSS group were part of the "higher OMERACT", while 4/13 (30.8%) were part of the "lower OMERACT".

Table III. OMERACT scores (for all patients) and frequencies of sonographic features (for focal lesions) in the L-pSS and nonL-pSS groups; sonographic features more frequently associated with L-pSS group are reported in bold.

US Features		MALT	NON-MALT	Δ%	p-value
OMERACT score	0	0	0	-	-
	1	0	30.8%	30.8%	0.0407
	2	28.6%	30.8%	10.2%	1.0000
	3	**71.4%**	**38.4%**	**33.0%**	**0.1283**
Echostructure	**Very Hypoechoic**	**88.9%**	**42.8%**	**46.1%**	**0.1057**
	Hypoechoic	11.1%	42.8%	31.7%	0.2615
	Isoechoic	0%	0%	-	-
	Hyperechoic	0%	14.3%	14.3%	0.4375
Inner appearance	**Homogeneous**	**77.8%**	**71.4%**	**6.4%**	**1.0000**
	Inhomogeneous	22.2%	28.6%	6.4%	1.0000
Shape	Round	0%	0%	-	-
	Oval	**88.9%**	**57.1%**	**31.8%**	**0.2615**
	Lobulated	11.1%	42.9%	31.8%	0.2615
Margins	**Well-defined**	**100%**	**85.7%**	**14.3%**	**0.4375**
	Ill-defined	0%	14.3%	14.3%	0.4375
Presence of septa	**Yes**	**88.9%**	**28.6%**	**60.3%**	**0.0349**
	No	11.1%	71.4%	60.3%	0.0349
Hypervascularity	**Yes**	**88.9%**	**42.9%**	**46.0%**	**0.1057**
	No	11.1%	57.1%	46.0%	0.1057
Posterior acoustic features	None	0%	14.3%	14.3%	0.4375
	Posterior shadowing	0%	14.3%	14.3%	0.4375
	Posterior enhancement	**100%**	**71.4%**	**28.6%**	**0.1750**

Focal areas

In L-pSS group, in 5/14 patients (35.7%) a diffuse enlargement of the SGs was present, without focal areas of parenchyma identifiable by different US features, while 9/14 low-grade lymphomas (64.3%) presented as focal abnormalities. Table IV summarises sonographic features of L-pSS focal lesions, described also below: 8/9 (88.9%) were very hypoechoic, while 1/9 (11.1%) were hypoechoic; their inner appearance was homogeneous in 7/9 (77.8%) and inhomogeneous in 2/9 (22.2%); 8/9 (88.9%) had an oval shape, while 1/9 (11.1%) was lobulated; 9/9 (100%) had well-defined margins; internal hyperechoic septa were found in 8/9 (88.9%) cases; colour-Doppler vascularisation was found in 8/9 (88.9%) cases; 9/9 (100%) showed a posterior acoustic enhancement.

By contrast, in the nonL-pSS group, in 6/13 patients (46.2%) a diffuse gland enlargement, without any focal lesion, was reported, while 7/13 patients (53.8%) presented a predominant focal lesion. Table II summarises sonographic features of nonL-pSS focal lesions, described also below: 3/7 (42.9%) were very hypoechoic, 3/7 (42.9%) were hypoechoic, while 1/7 was hyperechoic (14.2%), with an inner appearance that was homogenous in 5/7 (71.4%) and inhomogeneous in 2/4 (28.6%); 4/7 (57.1%) had an oval shape and 3/7 (42.9%) were lobulated; 6/7 (85.7%) had well-defined margins while 1/7 (14.3%) had ill-defined margins; internal hyperechoic septa were present in 2/7 (28.6%) cases; colour-Doppler vascularisation was found in 3/7 (42.9%) cases; 5/7 (71.4%) showed a posterior acoustic enhancement, 1/7 (14.3%) showed a posterior acoustic shadowing, while 1/7 (14.3%) showed neither.

List of features "suspicious" for salivary gland NHL in pSS

Based on the above reported US findings, the features more frequently as-

Table IV. L-pSS group. OMERACT score and sonographic features of focal lesions, when present, are reported for each of the fourteen patients included.

Patient	OMERACT score	Focal Lesion	Echostructure (FL)	Inner Appearance (FL)	Shape (FL)	Margins (FL)	Presence of Septa (FL)	Hypervascular (FL)	Posterior acoustic features (FL)
#14	2	Yes	Hypoechoic	Inhomogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#15	3	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	No	No	Posterior enhancement
#16	2	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#17	3	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#18	2	Yes	Very hypoechoic	Homogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#19	3	No	-	-	-	-	-	-	-
#20	3	No	-	-	-	-	-	-	-
#21	3	Yes	Very hypoechoic	Homogeneous	Lobulated	Well-defined	Yes	Yes	Posterior enhancement
#22	3	Yes	Very hypoechoic	Inhomogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#23	3	No	-	-	-	-	-	-	-
#24	2	No	-	-	-	-	-	-	-
#25	3	Yes	Very Hypoechoic	Homogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#26	3	Yes	Very hypoechoic	Homogeneous	Oval	Well-defined	Yes	Yes	Posterior enhancement
#27	3	No	-	-	-	-	-	-	-

sociated with NHL of the major SGs in pSS (in bold in Table III) were:

- in general: 1) OMERACT grade 3;
- in case of focal areas: 2) Very hypoechoic; 3) Homogenous; 4) Oval shape; 5) Well-defined margins; 6) Presence of septa; 7) Colour-Doppler vascularisation; 8) Posterior Acoustic Enhancement.

Therefore, these 8 features were considered "suspicious" for major SGs lymphoma in pSS.

Differentiation of NHL and non-NHL lesions with focal appearance

The simultaneous presence of 6 or 7 of the 8 features "suspicious" for SGs lymphoma was significantly higher in the L-pSS group, compared to the nonL-pSS group (for 6/8 simultaneous features: 88.9% *vs*. 28.6%, p=0.034; for 7/8 simultaneous features: 77.8% *vs*. 14.3%, p=0.040).

With respect to focal lesions, the comparison of the frequencies of simultaneous "suspicious" features for both groups are summarised in Table V and in Figure 1.

In the L-pSS group, specifically, for focal lesions, up to 5/8 "suspicious" features were simultaneously present in 100% of cases, 6/8 in 88.9%, 7/8 in 77.8%, while 8/8 suspicious features were simultaneously present in only 33.3%.

By contrast, in the nonL-pSS group, for focal lesions, 3/8 "suspicious" features were simultaneously present in 85.7% of cases, 4/8 in 71.4%, 5/8 in 57.1%, 6/8 in 28.6%, 7/8 in 14.3%, while no lesion presented all 8/8 "suspicious" features at the same time.

Table V. The frequency of simultaneous sonographic suspicious features (up to eight) in the L-pSS and nonL-pSS group and their difference are reported. The difference between L-pSS and nonL-pSS groups is significant when 6 or 7 "suspicious" features are simultaneously present.

Simultaneous suspicious features	L-pSS	95% C.I. (L-pSS)	nonL-pSS	95% C.I. (nonL-pSS)	Δ%	p-value
1	100%	0.6637 - 1.0000	85.7%	0.4213 - 0.9964	14.3%	0.437
2	100%	0.6637 - 1.0000	85.7%	0.4213 - 0.9964	14.3%	0.437
3	100%	0.6637 - 1.0000	85.7%	0.4213 - 0.9964	14.3%	0.437
4	100%	0.6637 - 1.0000	71.4%	0.2904 - 0.9633	28.6%	0.175
5	100%	0.6637 - 1.0000	57.1%	0.1841 - 0.9010	42.9%	0.063
6	88.9%	0.5175 - 0.9972	28.6%	0.0367 - 0.7096	60.3%	0.034
7	77.8%	0.3999 - 0.9719	14.3%	0.0036 - 0.5787	63.5%	0.040
8	33.3%	0.0749 - 0.7007	0%	0.0000 - 0.4096	33.3%	0.213

Some of our cases of the L-pSS group (with both diffuse and focal appearance) and of the nonL-pSS group are shown in Figures 2 to 4.

Discussion

In this paper, the possible value of SGUS was reported, for the first time, in the clinical work-up of pSS patients with an increased risk of lymphoma development.

Low-grade B-cell MALT lymphoma was the only NHL histotype found in our series of pSS patients with SGs enlargement and suspected NHL. This does not come as a surprise, considering that the association between chronic inflammation of one organ and the development of MALT lymphoma in that organ has been repeatedly described in literature, both in autoimmune diseases (*i.e*. pSS for major SGs, Hashimoto's disease for thyroid MALT) or when associated with definite infectious agents in other diseases, the most notable being Helicobacter Pylori infection related gastric MALT lymphoma (26-28). MALT lymphomas of major SGs can appear either with a diffuse or with a focal pattern.

Diffuse pattern

In all cases affected by MALT lymphoma, the underlying gland had moderate to severe structural changes, and was categorisable either as OMERACT 2 or 3 ("higher OMERACT" group in our study); the difference in terms of fre-

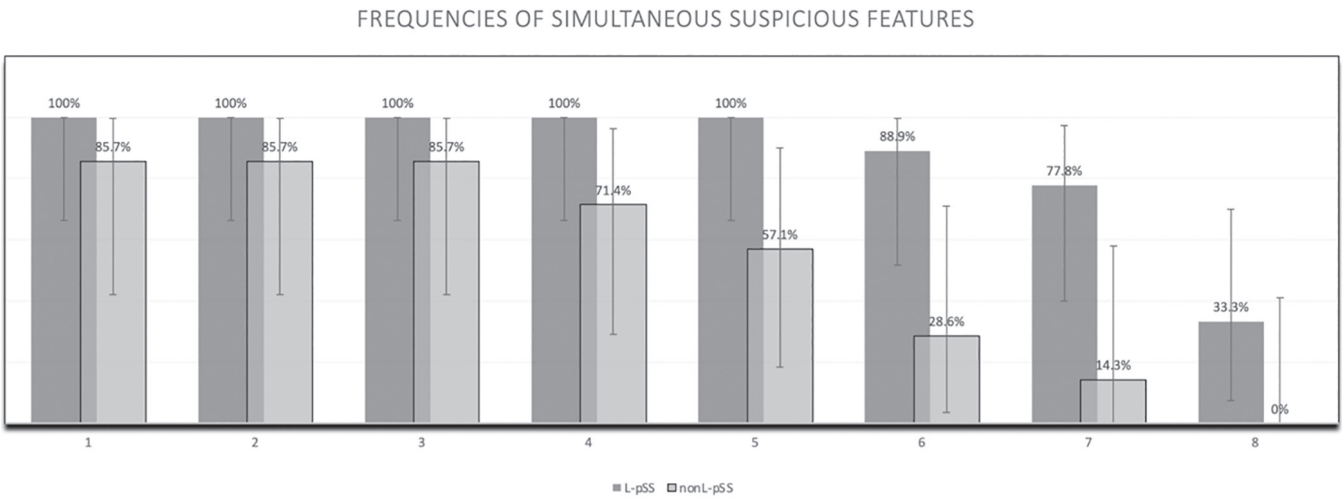

Fig. 1. The bar chart reports and compares the frequency of simultaneous sonographic suspicious features (up to eight) for the L-pSS and the nonL-pSS group, with their respective frequencies. 95% C.I.s are provided.

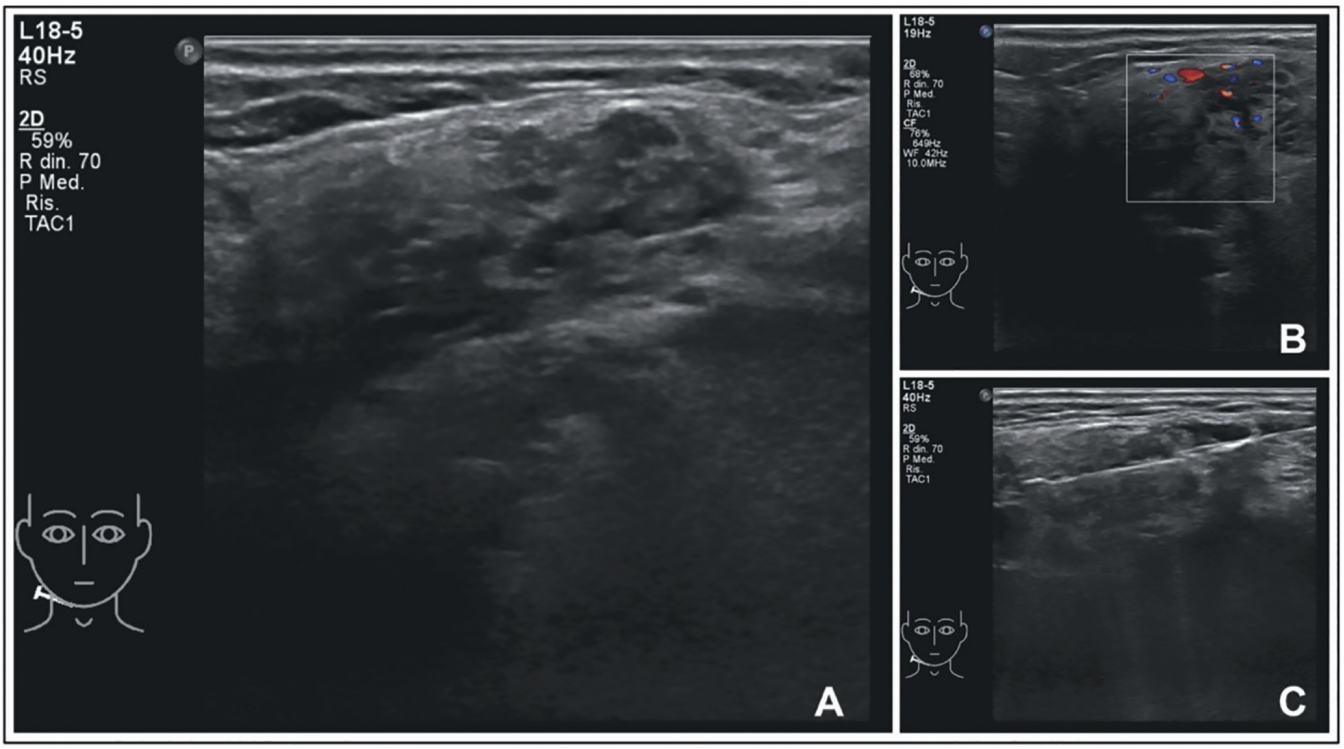

Fig. 2. Patient #20. The right submandibular gland was swollen and showed a diffusely inhomogeneous and hypoechoic echostructure (**A**), with vascularisation at the colour-Doppler examination (**B**). Non predominant focal lesion was present. A sampling of the gland parenchyma was performed with US-guided CNB (**C**) and the final diagnosis was of low-grade B-cell MALT lymphoma.

quencies of higher and lower OMERACT between L-pSS and nonL-pSS was statistically significant (100% *vs*. 69.2%; p=0.0407).

This was expected, since OMERACT grades 2 and 3 denote major SGs with more severe echostructural changes, which correlate with a higher burden of inflammation (25). As mentioned above, the association between chronic inflammation of one organ and the development of MALT lymphoma in that organ has been repeatedly described in literature, and the primary mechanisms of lymphomagenesis have been investigated and described. Recently, a review published by Stergiou *et al*. (29) outlined how in pSS the expansion of neoplastic cells in MALT lymphoma of the major SGs take place in lymphoepithelial lesions (LELs). LELs consist in histological findings characterised by infiltration and distortion of epithelial structures by aggregates of lymphoid cells, which can be seen in lymphoproliferative diseases (not only MALT lymphoma) but also in inflammatory states (30).

In fact, in the currently suggested model of lymphomagenesis, the autoantigen expression by the epithelium of the LEL in SGs of pSS patients, fuels the selection and the expansion of autoreactive B-cell clones with B-Cell

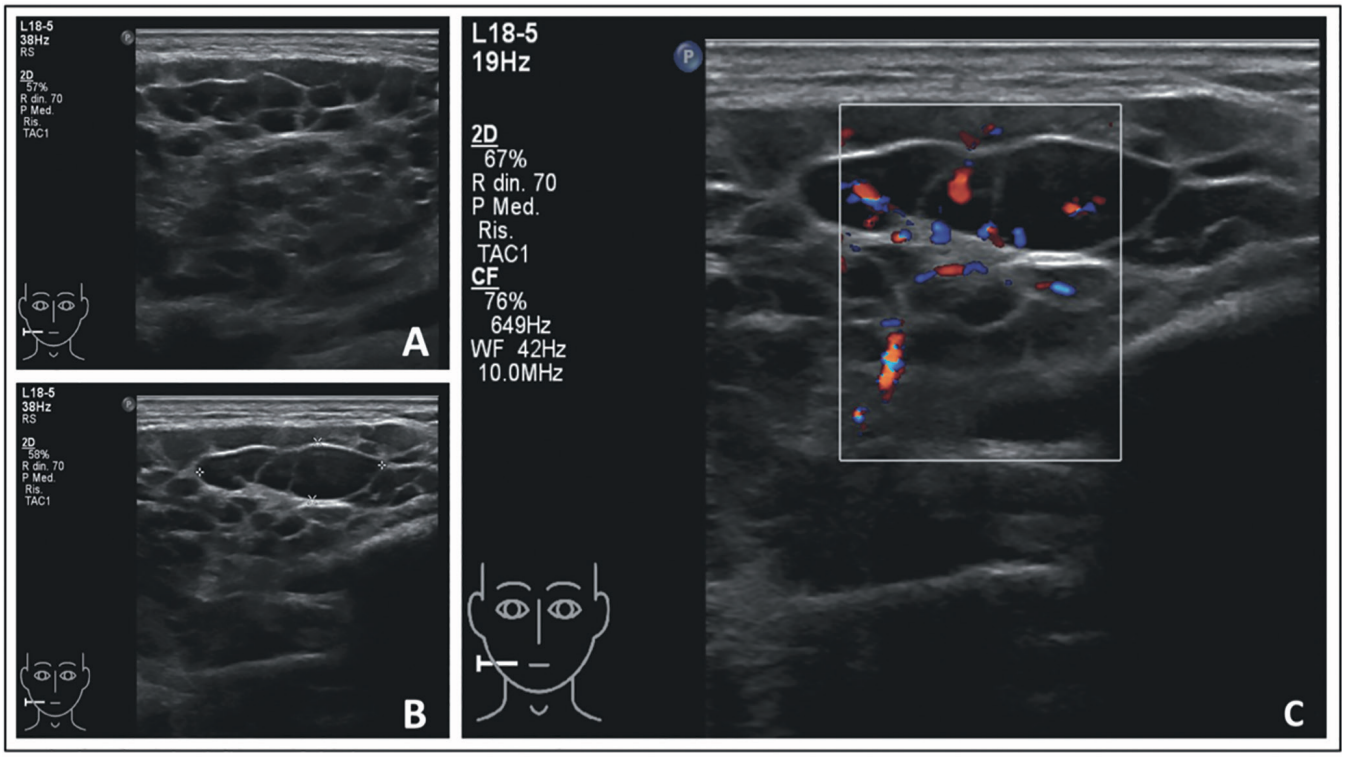

Fig. 3. Patient #17. The right parotid gland was swollen and showed a diffusely, very hypoechoic echostructure (**A**). Hyperechoic septa were present. A predominant focal lesion was detected (**B**), with signs of vascularisation at the colour-Doppler examination (**C**). 8/8 of the features we identified as suspicious were present. A tissue sample was obtained with US-guided CNB, and the final diagnosis was of low-grade B-cell MALT lymphoma.

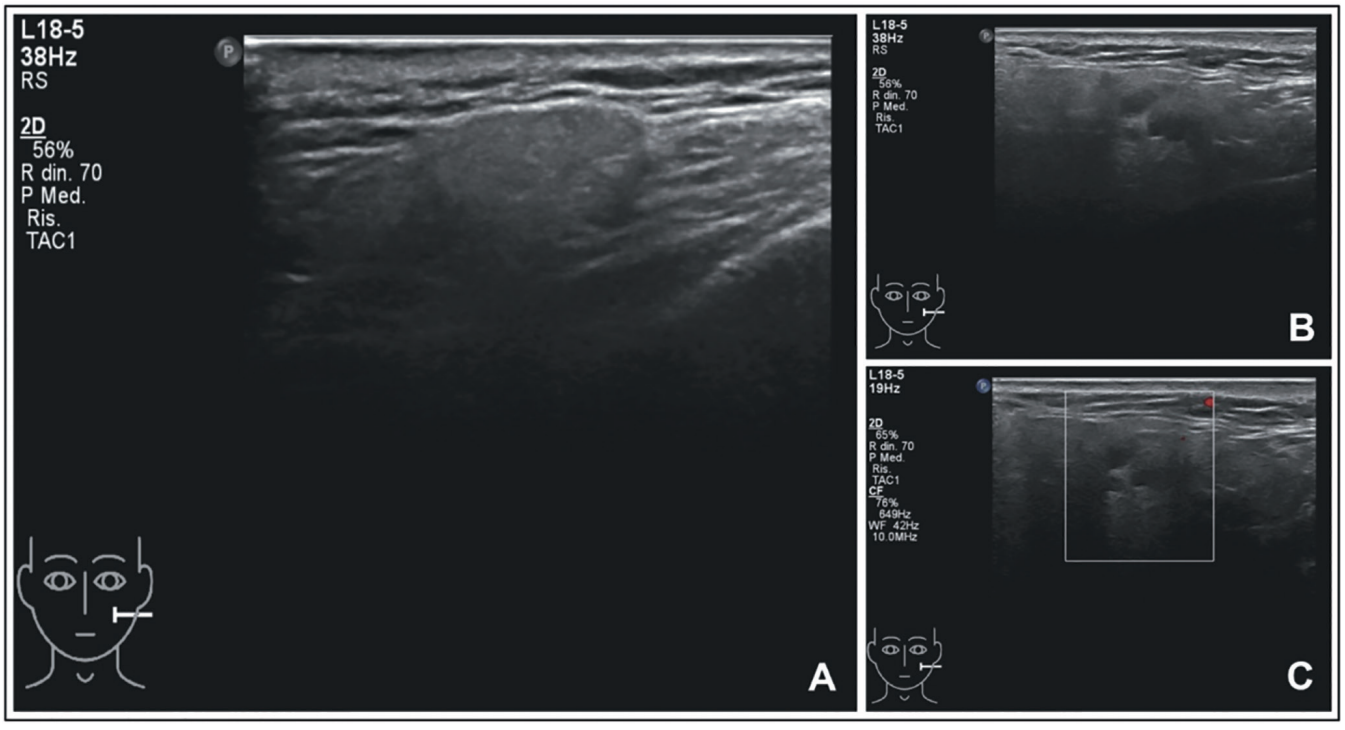

Fig. 4. Patient #5. The left parotid gland was swollen, with an overall minimal glandular inhomogeneity (**A**). A hypoechoic focal alteration was detected (**B**), with no signs of vascularisation at colour-Doppler examination. 4/8 of the features we identified as suspicious were present. A tissue sample was obtained with US-guided CNB, and the final diagnosis was of chronic inflammation with lymphoplasmacytic infiltration.

Receptors (BCR). These clones react to rheumatoid factor (RF), in a series of events that eventually lead these cells acquiring proliferative advantage, eventually malignant transformation and MALT lymphoma development.

Focal pattern

Considering the model of lymphomagenesis reported above, not surpris-

ingly a consistent proportion of cases presented focal lesions, probable macroscopic expression of a clonal, circumscribed proliferation.

To the best of our knowledge, there are no dedicated studies describing the radiological-pathological correlation of lymphoma of the major SGs; such correlation was made in other districts, *i.e.* for thyroid and breast lymphoma, in which dense infiltrates of lymphoid cells with various anomalies were generally correlated with hypoechoic lesions, not dissimilarly to our findings (31, 32), and it is not unreasonable to evaluate our results in light of this evidence. In our opinion, at least some of the focal areas we detected with SGUS and biopsied in our sample might have been the sonographic correlate of localised, expanding B-cell clones, as described in the model above.

This is further suggested by a recent study by Zabotti *et al*. (4), which evaluated the feasibility of CNB in pSS patients for the pathological evaluation of MALT lymphoma in major SGs and in which, for one of the patients, the tissue sample obtained from the focal lesion was found to be positive for MALT lymphoma at pathology, while the tissue sample obtained from the adjacent glandular parenchyma demonstrated the presence of diffuse chronic sialoadenitis.

Focal lymphomas presented more often as very hypoechoic areas, with an inner homogeneous appearance, oval shape, well-defined margins, colour-Doppler vascularisation, and posterior acoustic enhancement, in the context of a very inhomogeneous gland.

We also found that a SGUS pattern of presentation with six or seven "suspicious" characteristics significantly increased the probability of that lesion being a lymphoma rather than a non-lymphomatous condition.

Although a SGUS pattern showing all eight suspicious characteristics was more likely to be present in the L-pSS group compared to the nonL-pSS group (33.3% *vs*. 0%), the difference was not found to be statistically significant (p=0.213), reasonably as an effect of the relatively small study sample size.

Considered separately, only two features (OMERACT and presence/absence of septa) were found to be statistically different between L-pSS and nonL-pSS groups. We believe that, at least for some of the other features, the lack of a statistically significant difference could be due to the small sample size.

In any case, as reported above, as the number of features "suspicious" for SGs lymphoma increases, the diagnosis of SGs lymphoma itself becomes increasingly more likely.

Perspectives and limitations

Our paper suggests that low-grade B-cell MALT lymphomas (*i.e.* the usual NHL histotype in pSS) of the major SGs in pSS do have some distinctive US features, though with overlaps with other non-lymphomatous conditions. We believe that being able to reasonably suspect a lymphoma before biopsy in pSS patients does indeed have practical applications from a clinical point of view, helping to choose the best possible target and approach for biopsy itself.

This study has some limitations. The study population was small, and only the MALT NHL histotype could be investigated; a multivariable analysis could not be performed. However, this is a consequence of the low prevalence of the disease in the general population and, as far as we know, this is the largest series focusing on sonographic features in this selected pSS subgroup, thus representing a reasonable base for further studies. Second, we could not assess inter-reader agreement in interpreting SGUS findings and assessing the OMERACT score. However, for what concerns the OMERACT score, it has been proved to have excellent intra-Rater Reliability and substantial inter-Rater Reliability (33). We acknowledge that future studies on inter-reader agreement of SGUS findings should validate our results. On the other hand, our study reflected clinical practice in a tertiary referral centre for rheumatological diseases, with a dedicated radiologist with expertise in the field expected to perform examinations. We believe these results point out the relevance of larger investigation in this topic, for the final achievement of an improved diagnosis of lymphoma in pSS.

Conclusion

Lymphoma of the major SGs in patients with pSS associates with higher OMERACT scores (2 or 3) and presents with diffuse or focal pattern. For focal lesions, the association of an increased number of well-defined, "suspicious" sonographic features makes the diagnosis of lymphoma increasingly more likely. This may be relevant to plan a US-guided CNB of the major SGs in pSS patients with suspected lymphoma.

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