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Clinical science

Predicting lymphoma in Sjögren's syndrome and the pathogenetic role of parotid microenvironment through precise parotid swelling recording

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Abstract

Objective: Parotid swelling (PSW) is a major predictor of non-Hodgkin's lymphoma (NHL) in primary SS (pSS). However, since detailed information on the time of onset and duration of PSW is scarce, this was investigated to verify whether it may lead to further improved prediction. NHL localization was concomitantly studied to evaluate the role of the parotid gland microenvironment in pSS-related lymphomagenesis.

Methods: A multicentre study was conducted among patients with pSS who developed B cell NHL during follow-up and matched controls that did not develop NHL. The study focused on the history of salivary gland and lachrymal gland swelling, evaluated in detail at different times and for different durations, and on the localization of NHL at onset.

Results: PSW was significantly more frequent among the cases: at the time of first referred pSS symptoms before diagnosis, at diagnosis and from pSS diagnosis to NHL. The duration of PSW was evaluated starting from pSS diagnosis, and the NHL risk increased from PSW of 2–12 months to >12 months. NHL was prevalently localized in the parotid glands of the cases.

Conclusion: A more precise clinical recording of PSW can improve lymphoma prediction in pSS. PSW as a very early symptom is a predictor, and a longer duration of PSW is associated with a higher risk of NHL. Since lymphoma usually localizes in the parotid glands, and not in the other salivary or lachrymal glands, the parotid microenvironment appears to be involved in the whole history of pSS and related lymphomagenesis.

Keywords: Sjögren Syndrome, Parotid, Salivary swelling, Lymphoma

Rheumatology key messages

- The salivary glands have a key role in the lymphomagenesis in primary Sjögren's syndrome.
- Lymphoma often localizes in parotid gland; MALT histotype is the most frequent.
- Precise clinical recording of parotid swelling can improve lymphoma prediction in primary Sjögren's syndrome.

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Introduction

Primary SS (pSS) is an autoimmune and lymphoproliferative disease that affects mainly the salivary and lacrimal glands, with other glandular and systemic features [1–8], and predisposes to B cell non-Hodgkin's lymphoma (NHL) [9]. Extranodal marginal zone lymphoma (MZL) of the mucosa-associated lymphoid tissue (MALT) histotype [10, 11] appears to be the most frequent B cell NHL histotype in most studies [12–21]. Treatable infectious triggers of lymphoproliferation have been identified in peculiar microenvironments in MALT NHLs [10, 11], but the role of infection remains undefined in pSS [8, 22]. Lymphoma prevention in pSS remains a major unmet need.

Laboratory research in human minor salivary glands (SGs) indicates that the SG microenvironment plays a central role in autoimmune-related pathogenic events and expansion of B cells in pSS [5, 8, 22, 23]. Lymphoma, however, is localized much more frequently in the parotid glands than in the other SGs or lachrymal glands. In addition, parotid tissue from patients with pSS was rarely analysed in early non-malignant lesions in pSS [24] and is not included in pSS classification criteria [25]. Also, most clinical studies did not analyse in detail, during the whole natural history of the disease, parotid swelling (PSW), which can be considered a key predictor and clinical surrogate of local MALT acquisition [9, 26].

In this paper, we dissected the time of onset and duration of PSW during the whole history of pSS to analyse whether a more precise recording of PSW may improve the prediction of lymphoma. Further, we evaluated parotid localization of NHL at onset, which had to be provided in the same patients to explore the role of the parotid gland microenvironment up to the end of pSS-related lymphomagenesis.

Methods

Patients

A cohort of consecutive unselected patients with pSS who developed B cell NHL during follow-up was studied. Strict cooperation between rheumatologists, haematologists and pathologists from a limited number of reference centres was planned for the best retrospective data collection within the frame of the HarmonicSS programme [27].

Patients were referred to the Udine, Pisa, Athens Study Group and the study included cases available from Italy (Clinic of Rheumatology of the University Hospitals of Udine and Pisa) and Greece (Medical School of the University of Athens). Controls with pSS who did not develop NHL during the follow-up were selected from each participating centre using a random matching approach [28] and matched with cases (case: control = 1:1.5) for sex and age at pSS diagnosis. Both cases and controls were classified for pSS according to criteria published at the time of pSS diagnosis and subsequently confirmed by the latest classification criteria [25].

A dedicated database was created, and part of the clinical and laboratory data is shown in Table 1 and Supplementary Table S1, available at *Rheumatology* online. In any case, the aim of this study was not to investigate the possible predictors reported in these tables. The patient follow-up after pSS diagnosis lasted up to the development of NHL (cases) or the last follow-up visit available (controls).

Ethical statement

The study was performed according to the principles of the Declaration of Helsinki and subsequent amendments. The studies involving human participants were reviewed and approved by CEUR-2017-Os-027-ASUIUD. Each study participant or their legally authorized representative provided their written informed consent to participate in this study according to the Declaration of Helsinki.

History of glandular swelling

The histories of PSW, submandibular gland swelling, sublingual gland swelling or minor salivary gland (MSG) swelling as recorded by expert clinicians were studied for the complete course of pSS, and lachrymal gland swelling was investigated as well. The presence of swelling was diagnosed by clinical experts based on physical examinations [29] and based on anamnesis at symptom onset, since this could only be referred. To precisely define the time(s) of SG swelling in each patient, from pSS first symptoms to NHL diagnosis (cases) or the last follow-up (controls), different time point evaluations were planned during the pSS disease course. Thus, SG swelling was studied for both cases and controls if it occurred in any of the following circumstances:

i) at pSS symptom onset, as one of the first manifestations of pSS noted by the patient, documented in the clinical chart, and confirmed by an expert medical doctor at the time of the present study;
ii) at pSS diagnosis;
iii) at any time (i.e., at whatever moment) during the entire follow-up period, starting from pSS diagnosis to NHL diagnosis (cases) or to the last follow-up visit (controls); in controls presenting glandular swelling, lymphoma was always excluded;
iv) only late, such as swelling only within the last year before NHL diagnosis and/or at the time of NHL diagnosis, but never before the entire previous pSS history (cases).

Furthermore, because a different duration of salivary/lachrymal swelling could be related to NHL development differently [4], duration was studied from pSS diagnosis to NHL diagnosis (cases) or the last follow-up (controls), while the duration of swelling at pSS onset was not precisely quantified by the patient. The duration of glandular swelling was then categorized as (i) episodic and short duration (<2 months), (ii) episodic and prolonged duration (≥2 months but <12 months), or (iii) chronic (lasting ≥12 months). If different patterns of either the time of occurrence or duration of glandular swelling during the pSS clinical course were present in the history of the same patient, they were all recorded and evaluated.

NHL localization at the onset

The diagnosis and histotype of NHL were established in all cases by standard bioptic and pathological procedures [30]. Tissue biopsy was performed in nodal and/or extranodal sites at the time of NHL diagnosis, according to the clinical manifestations and imaging results as evaluated by an expert clinician. A bone marrow biopsy was always done. Biopsy specimens were evaluated by the local referent haemopathologist in each of the three centres and were always revised in this study when previously evaluated by another pathologist.

Table 1 Clinical data at the time of primary SS diagnosis

Feature	Cases	Controls	*P*-value
Sex F, *n*/N, %	129/144 (89.58)	198/222 (89.19)	0.905
Age at pSS diagnosis, mean (S.D.), years	50.3 (13.4)	48.8 (12.4)	0.264
Follow-up, median (range), years[a]	4 (0–30)	15 (2–42)	<0.001
Anti-SSA, *n*/*N* (%)	107/141 (75.89)	178/221 (80.54)	0.291
Anti-SSB, *n*/*N* (%)	71/142 (50.00)	93/219 (42.47)	0.160
Rheumatoid factor, *n*/*N* (%)	95/135 (70.37)	103/209 (49.28)	<0.001
Cryoglobulinemia, *n*/*N* (%)	37/127 (29.13)	12/176 (6.82)	<0.001
Type I	0/127 (0.00)	0/176 (0.00)	<0.001
Type II	31/127 (24.41)	5/176 (2.84)	
Type III	2/127 (1.57)	4/176 (2.27)	
Non-determined	4/127 (3.15)	3/176 (1.70)	
Low C4, *n*/*N* (%)	63/128 (49.22)	60/217 (27.65)	<0.001
Leucopenia, *n*/*N*	32/127 (25.20)	26/212 (12.26)	0.002
Lymphopenia <1500/μl, *n*/*N* (%)	50/103 (48.54)	81/196 (41.33)	0.232

Follow-up: from pSS diagnosis to non-Hodgkin lymphoma diagnosis (cases) or the last follow-up visit (controls). [a]By excluding the 39 cases with pSS diagnosis formulated at the time of lymphoma diagnosis, the median follow-up of cases was 7 years (range 1–30), with $P < 0.001$. F: female; pSS: primary SS.

If needed, their histological slides or electronic images were sent to the central referent pathologist of the study (M.P.). MZL B cell NHL was further distinguished into MZL of MALT whenever MALT localization was demonstrated by tissue biopsy and into nodal or splenic MZL when the involvement of MALT was lacking.

The localization of NHL as isolated nodal, isolated extranodal or both was indicated by physical examination and imaging workup, including abdomen–thorax–neck CT and ultrasound imaging of every patient. MRI and/or PET-CT scanning was used whenever deemed necessary. In addition, a positive biopsy was needed in at least one extranodal site to establish the extranodal NHL localization (alone or in combination with a nodal localization) or in the lymph nodes to assess an isolated nodal NHL localization.

Finally, the NHL stage was evaluated according to Ann Arbor criteria [31].

Statistical analysis

Continuous data were reported as mean (S.D.) or median and range as appropriate, while categorical data were summarized as percentages and absolute frequencies. Student's *t*-test or the Mann–Whitney test was performed to compare continuous variables. To compare categorical variables, Pearson's χ^2 test or Fisher's exact test, whichever was appropriate, was performed. Odds ratio (OR) and CI were reported. A logistic regression model was computed to estimate the association of PSW, focus score, lymphoepithelial lesions and germinal centres with NHL, adjusted for the pSS disease duration, which was evaluated starting from pSS diagnosis.

Results

Patients

One hundred and forty-four NHL pSS-related cases were included in this study; 129 were females (89.58%), while 15 were males (10.42%). The mean (S.D.) age of the patients was 50.3 (13.4) and 55.9 (12.5) years at the time of pSS or lymphoma diagnosis, respectively. The median follow-up time from pSS diagnosis to NHL diagnosis was 4 years (range 0–30) (Table 1).

The patients in the control group numbered 222: 198 were females (89.19%) and 24 were males (10.81%). The sex ratio, as well as the mean age at pSS diagnosis, was not statistically different among cases and controls. Further data are reported in Table 1. At the time of pSS diagnosis, a statistically significant difference was found between cases and controls in some laboratory tests investigated, including rheumatoid factor positivity, cryoglobulinaemia, low C4 and leukopenia. MSG biopsies performed at pSS diagnosis and available for revision showed a significantly higher detection of germinal centres and lymphoepithelial lesions in the cases compared with the controls, while the focus score values were increased though non-significantly (Supplementary Table S1, available at *Rheumatology* online) [32]. A pSS was diagnosed concomitantly with NHL in 39/144 cases (27.1%), and the haematologists were the initial referent specialists for them, crucial for case observation.

History of glandular swelling

In general, PSW swelling was much more frequent than the swelling of the submandibular glands, MSGs and lachrymal glands, and this occurred in both the cases and the controls. In detail, the swelling of the submandibular glands, the MSGs and the lachrymal glands occurred in 9/144, 1/144 and 6/144 of the cases, respectively, and in 3/222, 0/222 and 0/222 of the controls, respectively. The swelling of the sublingual SGs was never detected in either group. In addition, PSW was usually associated with such rare aforementioned swelling of the other glands. In detail, PSW was simultaneously present in eight of the nine cases and two of the three controls with submandibular swelling, in the one case with swelling of the MSGs (1/1) and in five of the six cases with swelling of the lachrymal glands. For this reason, when considering both statistical issues (because the inclusion of rare events leads to less precise estimates) and easier recording, PSW alone was used in the subsequent statistical analyses (Table 2). Cases with parotid swelling had a mean age of 56.1 (12.7) years *vs* a mean age of 56.7 (12.2) years in cases without parotid swelling ($P = 0.814$). Further data can be found in Supplementary Data S1, available at *Rheumatology* online.

Time of occurrence of PSW

PSW at pSS symptom onset was recorded in 59/141 of the cases (41.84%) *vs* 34/222 (15.32%) of the controls (OR: 4.47, 95% CI: 2.29, 8.73; $P < 0.001$). PSW at pSS diagnosis

Table 2 History of glandular swelling

Feature	Cases, *n*/*N* (%)	Controls, *n*/*N* (%)	OR (95% CI)[a]	*P*-value
Time of occurrence of PSW				
At pSS symptoms onset	59/141 (41.84)	34/222 (15.32)	4.47 (2.29, 8.73)	<0.001
At pSS diagnosis	74/141 (52.48)	31/220 (14.09)	6.30 (3.26, 12.16)	<0.001
At any time	108/139 (77.70)	60/222 (27.03)	10.66 (5.66, 20.09)	<0.001
Only late swelling	32/141 (22.70)			
Duration of PSW				
Episodic <2 months	28/140 (20.00)	38/222 (17.12)	1.74 (0.85, 3.57)	0.128
Episodic 2–12 months	65/141 (46.10)	19/222 (8.56)	10.41 (4.77, 22.68)	<0.001
Chronic	63/140 (45.00)	6/222 (2.70)	34.58 (11.08, 107.87)	<0.001

[a] Adjusted for disease duration; furthermore, by excluding the 39 cases with pSS diagnosis formulated at the time of lymphoma diagnosis, the significance <0.001 or non-significance of the *P*-value remained unchanged. pSS: primary SS; PSW: parotid swelling.

was recorded in 74/141 of the cases (52.48%) *vs* 31/220 (14.09%) of the controls (OR: 6.30, 95% CI: 3.26, 12.16; $P < 0.001$). PSW at any time, meaning from pSS diagnosis (included) to NHL diagnosis (included, for cases) or to the last follow-up (for controls) was recorded in 108/139 (77.70%) of the cases *vs* 60/222 (27.03%) of the controls (OR: 10.66, 95% CI: 5.66, 20.09; $P < 0.001$). PSW only late (for cases), meaning only in the year before NHL or at NHL diagnosis but never before, occurred in 32/141 (22.70%) of the cases.

Duration of PSW

Episodic PSW of short duration (<2 months) was present in 20/140 (14.28%) of the cases *vs* 38/222 (17.11%) of the controls (OR: 1.74, 95% CI 0.85, 3.57; $P = 0.128$). Episodic PSW of prolonged duration (2–12 months) was present in 65/141 (46.10%) of the cases *vs* 19/222 (8.56%) of the controls (OR 10.41, 95% CI 4.77, 22.68; $P < 0.001$). Chronic PSW (≥12 months) was present in 63/140 (45.00%) of cases *vs* 6/222 (2.70%) of controls (OR: 34.58, 95% CI 11.08, 107.87; $P < 0.001$) (Table 2).

Non-Hodgkin's lymphoma

NHL histotype

The MZL histotype was much more frequent, occurring in 83.33% of the cases. In detail, the prevalence of extranodal MZL of MALT was 75%, while nodal MZL and splenic MZL occurred in 6.25% and 2.08% of the cases, respectively. Diffuse large B cell lymphoma (DLBCL) was the second, though much less frequent, NHL histotype at onset (11.81%). The rarer NHL histotypes were follicular lymphoma (2.78%), lymphoplasmacytic lymphoma (1.39%) and mantle cell lymphoma (0.69%) (Table 3).

NHL stage and localization at the onset

The Ann Arbor stages of NHL at onset were stage I in 47.18% of the cases, stage II in 15.49%, stage III in 6.34%, and stage IV in 30.99%. NHL localization is reported in more detail in Table 3. An extranodal localization of NHL at onset, alone or associated with concomitant nodal localization, was observed in 88.19% (127/144) of the cases. This localization was strictly associated with the MZL of the MALT histotype ($P < 0.0001$). Furthermore, most of the NHLs (65.28%; 94/144) were isolated extranodal, not presenting any nodal localization at the onset.

By contrast, isolated nodal involvement was present in a small minority of pSS-associated NHLs (11.81%; 17/144) (Table 3). Of these, 6/17 had PSW at pSS onset, 11/17 had PSW at any time from pSS diagnosis to NHL diagnosis and 9/17 at NHL diagnosis. Parotid biopsy was, however, not performed in these cases with isolated nodal NHL and PSW. The differences in PSW occurrence at any time in cases with either isolated extranodal NHL (74/91; 81.3%) or extrandodal ± nodal NHL (97/122; 79.5%), *vs* cases with isolated nodal NHL (11/17; 64.7%), were both non-significant.

Table 3 Characteristics of non-Hodgkin's lymphoma

Feature	
Sex F, *n*/*N* (%)	129/144 (89.58)
Age at NHL diagnosis, mean (S.D.), years	55.9 (12.5)
Follow-up from pSS diagnosis to NHL diagnosis, median (range), years	4 (0–30)
NHL histotype, *n*/*N* (%)	
MZL	120/144 (83.33)
MZL MALT	108/144 (75.00)
MZL primary splenic	3/144 (2.08)
MZL primary nodal	9/144 (6.25)
DLBCL	17/144 (11.81)
Follicular	4/144 (2.78)
Lymphoplasmacytic	2/144 (1.39)
Mantle cell	1/144 (0.69)
NHL clinical localization, *n*/*N* (%)	
Isolated nodal NHL	17/144 (11.81)
Isolated extranodal NHL	94/144 (65.27)
Extranodal ± nodal NHL	127/144 (88.19)
Parotid glands	83/144 (57.64)
Submandibular glands	5/144 (3.47)
Minor salivary glands	3/144 (2.08)
Salivary glands (whole)	90/144 (62.5)
Lachrymal glands	6/144 (4.17)
Salivary or lachrymal glands	95/144 (65.97)
Stomach	12/144 (8.33)
Lung	10/144 (6.94)
Spleen	5/144 (3.47)
Skin	2/144 (1.39)
Breast	2/144 (1.39)
Ocular adnexa	2/144 (1.39)
Thymus	2/144 (1.39)
Ovary	1/144 (0.69)
Large intestine	1/144 (0.69)
Liver	1/144 (0.69)
Larynx	1/144 (0.69)
Bone marrow NHL positivity	30/144 (20.83)
NHL stage, *n*/*N* (%)	
I	67/142 (47.18)
II	22/142 (15.49)
III	9/142 (6.34)
IV	44/142 (30.99)

DLBCL: diffuse large B cell lymphoma; F: female; MALT: mucosa-associated lymphoid tissue; MZL: marginal zone lymphoma; NHL: non-Hodgkin's lymphoma; pSS: primary SS.

Among the different extranodal NHL localizations, the most frequent one was of the parotid glands (57.64%; 83/144), which was also strictly associated with the MZL of the MALT histotype ($P < 0.001$). Lymphoma localization in the submandibular glands (3.47%), MSGs (2.08%) or lachrymal glands (4.17%) was much rarer. Overall, a salivary and/or lachrymal NHL localization at diagnosis was present in 65.97% of the cases (95/144). Other extranodal NHL localizations include the gastric mucosa (8.33%); the lung (6.94%); the skin, breast, ocular adnexa and thymus (1.39% or 2/144 each); and the ovary, large intestine, liver and larynx (0.69% or 1/144 each) (Table 3). NHL localization in the spleen, defined as an extranodal site [33], was observed in 3.47% or 5/144 cases: 3/5 were splenic MZLs localized in the spleen and the bone marrow, 1/5 MZL involved both the spleen and the parotids, while 1/5 was a gastric DLBCL with splenic NHL localization. Bone marrow involvement was present in 20.83% (30/144) of the cases. In cases with extranodal MZLs of MALT, bone marrow positivity was 15.31% (17/111) and was associated with mixed cryoglobulinaemia in 47.06% (8/17).

Discussion

The present study of a large series of 144 patients with pSS who developed B cell NHL revealed for the first time the importance of very precise monitoring of a key predictor of lymphoma evolution in pSS, specifically PSW, by recording its time of onset and duration. PSW proved to be a very early predictor of lymphoma, and a differential risk for different times of onset and duration was evident. We report another original observation, which could be drawn out only because the same series of patients were analysed for NHL localization. The parotid gland microenvironment in particular (rather than the SG or lachrymal microenvironment in general) plays a pathogenetic role in the final step of pSS-related lymphomagenesis since it is directly involved in the development of NHL with a large prevalence. Thus, together with the prediction of NHL based on very early PSW, the parotid gland appears as a key microenvironment during the whole lymphomagenesis in pSS. Both observations have relevant implications, in our opinion, ameliorating clinical practice and highlighting a less-studied tissue for possible research.

Findings on SG swelling in pSS will be discussed first. Several studies have demonstrated that PSW is caused by the heavier acquisition of MALT in pSS, with the local clonal B cell expansion [4, 5, 23, 26]. In a recent preliminary study [34], NHL occurring in the follow-up of pSS was associated with both persistent salivary gland swelling, either parotid or submandibular, and mixed cryoglobulinaemia, i.e. the other major predictor of lymphoma in pSS, linked with MALT acquisition [35, 36].

As herein underscored in our study, parotid glands deserve particular consideration in pSS, since they are swollen much more frequently at all points of the pSS history of cases, from pSS diagnosis to NHL onwards, than the submandibular, MSG or lachrymal glands. Increased predisposition of the parotid glands to local infection, and local microbiome and immune factors may be implicated [37, 38].

PSW was significantly more frequent in cases developing NHL than in controls, at any time of follow-up, consistent with the predisposing pathogenetic role of a changing parotid microenvironment, possible at any time during pSS history. Thus, as a first consideration, a careful monitoring of PSW is needed during the whole course of pSS. Secondly, since the controls with PSW did not develop NHL, a parotid microenvironment favouring lymphoma progression in cases, and qualitatively different from that of controls, may be also implicated. Such a 'risky PSW', underlying a 'risky parotid microenvironment', can be associated with additional risk factors for NHL in pSS [9], as also observed in this study (Table 1), and some of these additional factors, such as cryoglobulinaemia and peculiar RF idiotypes, may indeed underlie a malignant or pre-malignant B cell expansion within the parotid glands themselves [3, 4, 9, 22].

We also distinguished for the first time that PSW can be considered either more or less risky for NHL only if precise information on both its time of onset and duration is collected. Of note, the correlation with NHL was significantly increased at any time of PSW onset and was also the first symptom of pSS, while the diagnosis of pSS is often delayed for several years in an adult, in contrast with a child [39]. PSW as an initial symptom may relate to a previous local infection with the initial acquisition of MALT. PSW may also occur only very proximal to NHL development (1 year or less); but in this case, rather than being a true NHL predictor, it may simply reflect the development of NHL [9]. Precise information is required on the duration of PSW given that the sole persistent PSW (≥2 months), either episodic of prolonged duration (2–12 months) or chronic (≥12 months; showing an even higher odds ratio) was significantly associated with NHL development, while short-term episodic PSW (<2 months) was not (Table 2). Importantly, episodic long duration or chronic PSW was rare in this study's controls (<9% and <3%, respectively), so these clinical findings are now better defined, together with mixed cryoglobulinaemia, as a red flag for lymphoma risk in pSS [10].

We recommend the yearly evaluation of lymphoma predictors [10] in any pSS patient, and a baseline SG ultrasound exam, including instrumental PSW evaluation. Repetition of a yearly SG ultrasound (or even more frequently, if needed) is advisable in patients with NHL risk factors or PSW, with major SG biopsy available [40, 41]. Finally, if a blood monoclonal B cell expansion is demonstrated, such as monoclonal gammopathy of undefined significance (MGUS) or type I cryoglobulinaemia, evaluation of risk factors for increased risk of haematological malignancies would be needed [42], with the cooperation of the haematologist.

We strongly advise biopsy of the parotid glands [40] as well as of any other salivary and lachrymal gland that is persistently swollen in pSS driven by clinical suspicion and at any time during the pSS history, and also biopsy of non-swollen glands, if the SG ultrasonographic pattern implicates an increased NHL risk. The advantages of ultrasound-guided SG biopsy in pSS could encourage more widespread use of this biopsy in pSS [40, 43]. This tool allows focused biopsy also in the absence of parotid or submandibular gland swelling, with an accurate sonographic measurement of the glandular volume at that time [29]. The use of minor salivary gland biopsy to detect lymphoma in pSS, recently proposed [44], has very low invasiveness, but also major limitations, in our opinion, mainly the low sensitivity and the possibility of missing, even if positive, primary sites of lymphoma elsewhere in areas not biopsied (e.g. the parotid glands themselves) [44].

This study investigated the involvement of the SG microenvironment in the last events of pSS-related lymphomagenesis.

This had to be demonstrated in the same series of patients together with PSW as an early predictor of NHL to justify our second main conclusion (i.e. the likely, relevant role of the parotid microenvironment in the whole pSS-related lymphomagenesis). Preferential localization of NHL at its onset in the parotid glands (57.64%) was found, as expected based on the literature, and the parotid localization was significantly associated with the MALT MZL histotype ($P < 0.001$) [12–21]. The importance of the local microenvironment is well recognized in MALT lymphomagenesis, with local infectious agents implicated in local ongoing antigen stimulation of T cells, local hyperexpression of B cell growth factors and autoreactivity of B cells originating in the MALT NHL [10, 11]. The pathogenic role of initial infection has been hypothesized in pSS but remains unknown. Of note, bacterial and viral infections occur more commonly in the parotid glands, which have a lower rate of secretion and a less mucinous composition than submandibular glands [37]. In addition, parotid glands are even more frequently involved in paediatric than in adult pSS [39], and represent the only glands involved in juvenile recurrent parotitis [37]. Finally, pSS-related NHLs employ B cell immunoglobulin genes similar to B cell NHLs associated with the sialotropic HCV [45], and such NHLs frequently involve the parotid glands [46].

In any case, other microenvironments besides the parotids or the SGs may play a pathogenic role at least in the final steps of pSS-related lymphomagenesis, as reflected by the different MZL localizations documented in this study (Table 3) and consistent with the literature. Similarly to salivary and lachrymal glands, local factors like infection, microbiota and immune factors may be implicated. MZLs comprise malignant B cells of the marginal zone [10, 11], but MZL of MALT was noticed in this series much more frequently than a nodal or splenic MZL. DLBCL was the second most frequent NHL histotype in pSS, consistent with the hypothesis of a MALT linkage since evolution from MZL of MALT to DLBCL is possible [11, 47].

Different triggers may play a pathogenic role in different MALT NHL microenvironments [11] within the same patient with pSS [48, 49]. Recirculation of marginal zone B cells may occur [5, 47]. In this way, different exogenous antigens and/or autoantigens might stimulate MALT acquisition outside the SGs. In one paper, local antigen-driven B cell NHL of MALT in the lung is described in pSS. However, the B cell clone originating from lung NHL was already present in an antedating and non-malignant parotid myoepithelial sialadenitis and subjected to local antigen stimulation [49]. Another study supports the same concept for the gastric microenvironment and *H. pylori* in pSS [48]. Overall, pathogenic events of NHL may start in SGs but end in other sites in pSS.

Detailed information during a very long patient history, with full cooperation between haematologists, rheumatologists and pathologists, was required for this study. Although having the unavoidable limitation of being retrospective, this study overcomes some pitfalls of previous papers on the topic [12, 21], such as lower numbers of studied cases, paucity of detailed information on the key clinical surrogate of SG MALT acquisition in pSS (i.e. SG swelling), lack of earliest clinical and pathological data, analysis of only certain time points rather than the whole disease course, and, above all, lack of simultaneous evaluation of all the aforementioned issues in individual cases. The patients in this study were all strictly referred for a long time to the three referent cohorts [3, 4, 9, 21, 50].

Conclusion

In conclusion, PSW can be a better predictor of lymphoma in pSS if more detailed information is collected about its time of occurrence and duration. A precise and repeated clinical recording of PSW, together with the ultrasonographic evaluation of SGs, is thus recommended. Since the parotids are often involved in the final step of lymphomagenesis in pSS, due to the usual parotid localization of lymphoma itself, the parotid microenvironment is pathogenetically relevant in the whole history of pSS and related lymphomagenesis. Both these findings are important for clinical practice and research. Of note, putative aetiological agents of MALT autoimmunity and lymphoproliferation in pSS, highly hypothesized but still unknown, could be detected within parotids, starting from a very early disease.

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Data availability statement

The data will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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