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Original article

Characterization and outcomes of 414 patients with primary SS who developed haematological malignancies

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Abstract

Objective. To characterize 414 patients with primary SS who developed haematological malignancies and to analyse how the main SS- and lymphoma-related features can modify the presentation patterns and outcomes.

Methods. By January 2021, the Big Data Sjögren Project Consortium database included 11 966 patients fulfilling the 2002/2016 classification criteria. Haematological malignancies diagnosed according to the World Health Organization (WHO) classification were retrospectively identified.

Results. There were 414 patients (355 women, mean age 57 years) with haematological malignancies (in 43, malignancy preceded at least one year the SS diagnosis). A total of 376 (91%) patients had mature B-cell malignancy, nearly half had extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma) ($n = 197$), followed by diffuse large B-cell lymphoma (DLBCL) ($n = 67$), nodal MZL lymphoma ($n = 29$), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) ($n = 19$) and follicular lymphoma (FL) ($n = 17$). Rates of complete response, relapses and death were 80%, 34% and 13%, respectively, with a 5-year survival rate of 86.5% after a mean follow-up of 8 years. There were significant differences in age at diagnosis (younger in MALT, older in CLL/SLL), predominant clinical presentation (glandular enlargement in MALT lymphoma, peripheral lymphadenopathy in nodal MZL and FL, constitutional symptoms in DLBCL, incidental diagnosis in CLL/SLL), therapeutic response (higher in MALT lymphoma, lower in DLBCL) and survival (better in MALT, nodal MZL and FL, worse in DLBCL).

Conclusion. In the largest reported study of haematological malignancies complicating primary SS, we confirm the overwhelming predominance of B-cell lymphomas, especially MALT, with the salivary glands being the primary site of involvement. This highly-specific histopathological scenario is linked with the overall good prognosis with a 5-year survival rate of nearly 90%.

Key words: SS, haematological malignancy, lymphoproliferative disease, lymphoma, MALT

Rheumatology key messages

- 91% of haematological malignancies in primary SS are mature B-cell lymphomas.
- Their clinical outcome is driven by the neoplasia subtype, primary involved organ and presentation time.
- In 10% of the patients, the haematological malignancy might precede the diagnosis of SS.

Introduction

Patients with autoimmune diseases have a high risk of developing haematological malignancies, especially lymphomas [1]. Although the pathophysiology of this association is unknown, it is probably due to the interplay of individual genetic and environmental factors triggering a chronic inflammatory scenario characterized by persistent B-cell activation [2, 3]. Indeed, patients with primary SS have a 10- to 40-fold higher risk of developing lymphoma than healthy individuals [4]. The pathogenesis of SS is characterized by a chronic lymphocytic infiltration especially centered in the exocrine glands but also encompassing extraglandular tissues [5]. A sustained stimulation of B cells by autoantigens and immune complexes abnormally expressed in salivary and lachrymal glands has been postulated as an underlying pathogenic scenario that may predispose for development of malignancy. A multi-step pathogenic process follows, involving pro-oncogenic factors that could favour the transition from a benign B-cell process to a malignant proliferation [5].

Despite the evident association between haematological malignancy and primary SS, we still have a limited view of that association. The number of cases included in the main studies are often small and collected from single centres, and overwhelmingly centered on B-cell lymphomas. Focusing on the main studies published in the last 20 years in patients with primary SS, most reported 30–50 patients and only three described around 100 patients with lymphoma [6–20] (Supplementary Table S1, available at *Rheumatology* online).

In this study, we describe the main features and risk factors of 414 patients with primary SS who developed haematological malignancies, including a specific analysis of how certain features (lymphoma subtypes, organ primarily involved by the malignancy, systemic SS activity and timing of diagnosis) may influence the clinical presentation patterns and outcomes of the malignancy.

Patients and methods

The Big Data Sjögren Project Consortium is an international, multicentre registry established in 2014 to take a 'high-definition' picture of the main features of primary SS using worldwide data-sharing cooperative merging of pre-existing clinical databases from leading centres in SS from the five continents. The centres share a harmonized data infrastructure and conduct cooperative online efforts in order to refine already-collected data in

each centre [21]. By January 2021, the database included 11 966 patients fulfilling the 2002 AECG classification criteria [22] and/or the 2016 ACR/EULAR classification criteria [23]. Systemic involvement was retrospectively scored using the ESSDAI [24]. The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Haematological malignancy data

Haematological malignancies were diagnosed according to the World Health Organization (WHO) classifications [25–26]. We retrospectively collected: constitutional symptoms at diagnosis (fever, sweats and unexplained weight loss), site of confirmatory biopsy, bone marrow involvement, WHO classification, treatment, treatment response, relapse, time of follow-up and death. For extranodal lymphomas, the primary site of malignancy involvement was defined as the clinically dominant extranodal component, which requires diagnostic investigation and to which primary treatment must often be directed [27]. In all cases, the diagnosis was confirmed by a haematopathologist, and follow-up was provided by the multidisciplinary care team.

Statistical analysis

Descriptive data are presented as mean and S.D. for continuous variables and numbers and percentages (%) for categorical variables. We used χ^2 test and *t* test, according the type of variable. Logistic multivariate regression models adjusting for age at diagnosis and sex were constructed to analyse independent factors associated with mature B-cell malignancy subtypes [extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma (FL)], primary extranodal site [salivary glands *vs* those arising in other sites (when patients had both types of involvement, they were included in the salivary gland group)], and time of diagnosis of haematologic malignancy [prior to SS (diagnosed >1 year prior to SS diagnosis) or concurrent with/after SS diagnosis (diagnosed within <1 year of SS diagnosis), concomitantly, or during the follow-up of patients already diagnosed with SS)].

To identify predictors of lymphoma development, baseline features at the time of SS diagnosis were compared in patients with and without haematological malignancy following an age, sex and disease duration-matched 1:2 case-control design (excluding those patients diagnosed with haematological malignancy prior SS). The mean ESSDAI score measured before starting lymphoma treatment (at the time of diagnosis of haematological malignancy in patients already diagnosed with SS) was compared according to the therapeutic response categories (complete, partial, no response) and the survival (yes, no) and adjusted for the type of lymphoma and Ann Arbor Staging Classification.

We reported odds ratios (OR) and 95% CI. Time-to-event analyses for death are presented as Kaplan–Meier curves. The log-rank test was used to compare the survival curves. A two-tailed $P < 0.05$ was considered statistically significant. All analyses were conducted using the R v.3.5.0 for Windows statistical software package.

Results

Among the 11 966 patients with primary SS included in the Registry, 463 had a haematological malignancy. Of these patients, 49 were excluded because the diagnosis was not confirmed by a haematopathologist and/or fulfilment of the WHO classification was not available. Therefore, 414 patients (3.46%, 95% CI 3.13%, 3.79%) were finally included (355 women, mean age of 57.21 years); in 258 cases, the malignancy was diagnosed one year after the SS diagnosis (67 of whom were incident cases). Table 1 summarizes the main features related to haematological malignancies and Supplementary Table S2 (available at *Rheumatology* online), the main SS-related features at the time of primary SS diagnosis.

Characterization of haematological malignancies

The clinical presentation of the haematological malignancy included glandular enlargement ($n = 176$, 45.4%), constitutional symptomatology ($n = 126$, 34%) and peripheral lymphadenopathies ($n = 109$, 29.4%). Haematological malignancy was occasionally diagnosed in asymptomatic patients, either by an abnormal peripheral blood count ($n = 31$, 8.3%), incidental detection in imaging studies ($n = 2$, 0.5%), or by salivary gland biopsies ($n = 6$, three after parotid biopsy and three after minor salivary gland biopsy).

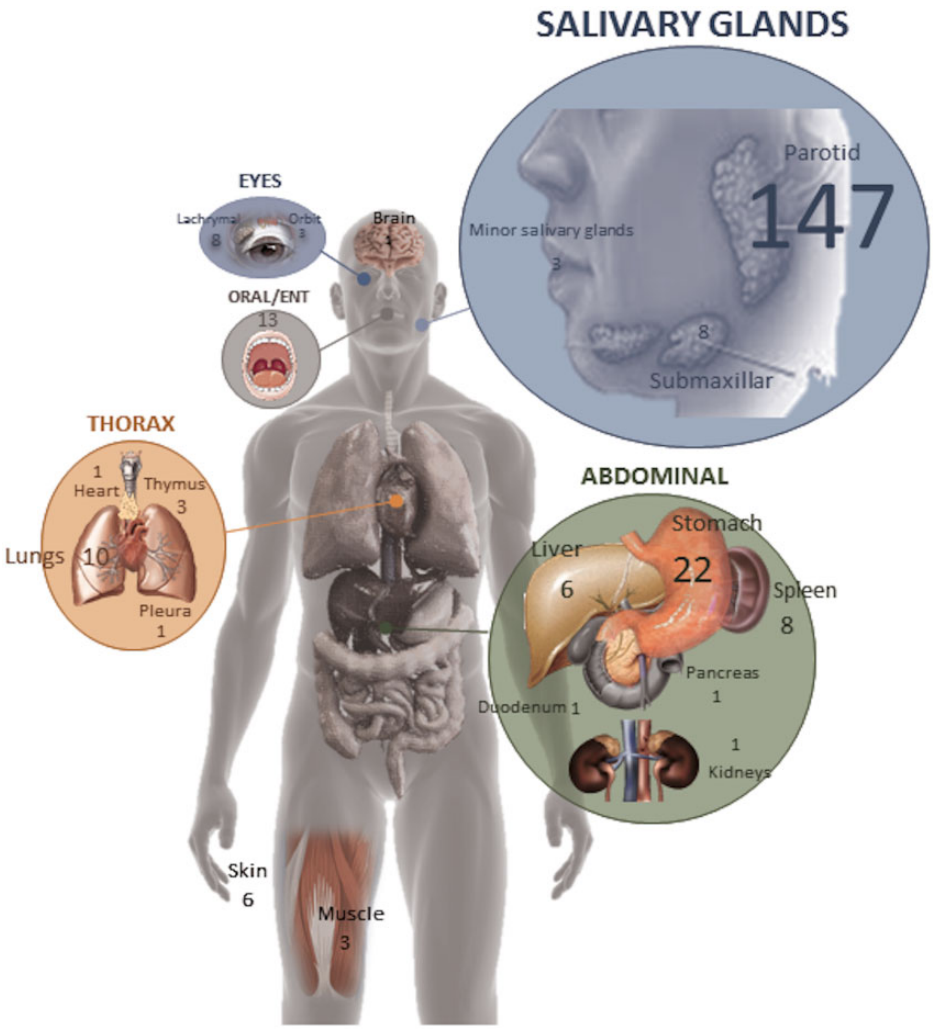
According to the WHO classification, 376 (91%) patients were classified as having mature B-cell malignancy, followed by myeloid neoplasia/acute leukemias ($n = 20$,5%), Hodgkin lymphoma ($n = 10$, 2%) and mature T and NK malignancy ($n = 8$, 2%) (Table 1). Among mature B-cell malignancies, nearly half the cases were diagnosed with MALT lymphoma ($n = 197$, 47.5%), followed by DLBCL ($n = 67$, 16.2%), nodal MZL lymphoma ($n = 29$, 7%), CLL/SLL ($n = 19$, 4.5%) and follicular lymphoma ($n = 17$, 4.1%) (Table 1). We have data about the site of confirmatory biopsy in 386 (93.2%) patients, with the parotid ($n = 147$, 36%) and lymph nodes ($n = 92$, 24%) being the most common organs biopsied (Table 1). Other exocrine glands were rarely affected (lachrymal glands in eight patients, submandibular glands in eight patients). Fig. 1 shows the distribution of the primary extranodal sites, and seven patients had more than one extranodal site affected (mean ESSDAI score of 17.1) including the parotid glands ($n = 6$), lungs ($n = 5$), and liver, stomach or lachrymal glands (one case each, respectively). Information about Ann Arbor Staging Classification of lymphoma was available in 320 patients: 21 (6.6%) were classified as stage I, 166

Table 1 Characterization and outcomes of hematological malignancy in 414 patients with primary SS

Epidemiology ($n = 414$)	*n*	%
Gender (women)	355	85.7
Ethnicity (white)	368	88.8
Age at SS diagnosis (mean, range)	52.4 years	10–87 years
Age at diagnosis of haematologic malignancy (mean, range)	57.2 years	21–91 years
Timing of diagnosis of haematologic malignancy		
Before SS diagnosis	43	10.1
Concomitant/after SS diagnosis	371	89.7
WHO classification ($n = 414$)		
Mature B-cell neoplasia	376	90.8
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	197	47.5
Diffuse large B-cell lymphoma (DLBCL)	67	16.2
Nodal marginal zone lymphoma	29	7.0
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	19	4.5
Follicular lymphoma	17	4.1
Other	37	8.9
NHL not classifiable (insufficient data for WHO class)	13	3.1
Myeloid neoplasias and acute leukemias	20	4.8
Hodgkin lymphoma	10	2.4
Mature T and NK neoplasia	8	1.9
Primary organ specific confirmation (386 patients)		
Exocrine glands (salivary, lachrymal)	176	45.3
Lymph nodes[a]	92	23.8
Bone marrow (only biopsied organ)	39	10.1
Digestive	25	6.4
ENT	12	3.1
Lungs	11	3.6
Peripheral blood	10	2.5
Spleen	5	1.2
Skin	6	1.5
Eye	3	0.7
Soft tissue/muscular	2	0.5
Thymus	3	0.7
Central nervous system	1	0.2
Kidney	1	0.2
First-line therapeutic approach (364 patients)		
Immunochemotherapy[b]	129	35.4
Chemotherapy alone[c]	58	15.9
Immunotherapy alone[d]	43	11.8
Other therapeutic interventions[e]	86	23.6
No therapeutic intervention ('watch and wait')	48	13.1
Malignancy outcomes		
First-line treatment response (281 patients)		
Complete response	225	80
Partial response	38	13.5
No response	18	6.4
Relapse ($n = 263$)	90	34.2
Death ($n = 365$)	47	12.8
Causes of death ($n = 39$)		
Cardiovascular	2	5.1
Infection	12	30.7
Haematologic malignancy progression	20	51.2
Other causes	5	12.8

[a]Lymph nodes: Inguinal 13 (14.1%), abdominal 6 (6.5%), axilar 7 (7.6%), cervical 30 (32.6%), mediastinal 5 (5.4%), retroperitoneal 2 (21.1%), non-specified 29 (31.5%). [b]Immunochemotherapy. Main regimens: R-CHOP ($n = 67$), RTX-CFM ($n = 11$), R-CVP ($n = 10$), RTX+chlorambucil ($n = 8$). [c]Chemotherapy alone. Main regimens: CHOP ($n = 19$), BR ($n = 15$), other ($n = 21$). [d]Immunotherapy alone. Main regimen: RTX ($n = 43$). [e]Including surgery and/or radiotherapy alone ($n = 65$), autologous transplantation ($n = 5$), only steroids ($n = 6$), only intrathecal chemotherapy ($n = 1$), intravenous immunoglobulins ($n = 1$), others ($n = 8$).

FIG. 1 Distribution of extranodal involvement by organ



(51.9%) as stage II, 37 (11.5%) as stage III and 96 (30%) as stage IV.

Among 281 patients with available data about therapeutic response (Supplementary Fig. S1, available at *Rheumatology* online), we observed complete response (CR) in 225 (80%), partial response (PR) in 38 (13.5%) and no response (NR) in 18 (6.4%) patients. R-CHOP was the immunochemotherapy regimen most commonly used; there was a trend towards a better survival rate in comparison with patients treated only with chemotherapy (CHOP), although the difference was not statistically significant (Supplementary Fig. S2, available at *Rheumatology* online). *Helicobacter pylori* was tested in 10 out of the 13 patients with gastrointestinal MALT lymphoma, of whom seven were positive and received eradication treatment. Relapses occurred in 90 (34.2%) patients who showed a complete or partial response to the first-line therapeutic approach. Among them, 14 showed a transition to a different WHO subtype, overwhelmingly as a progression to high-grade lymphomas (DLBCL 10 patients, peripheral T-cell lymphoma two patients).

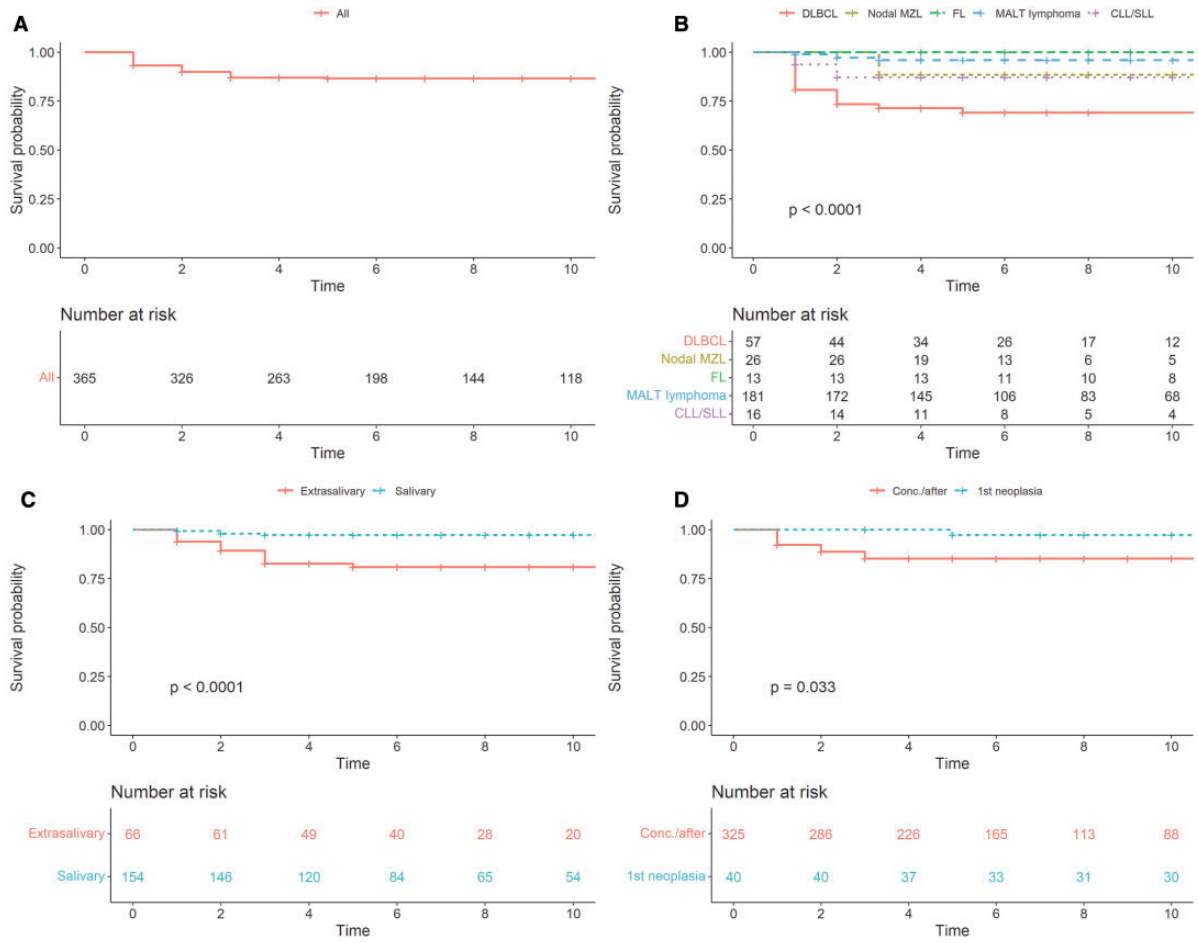
Information about the follow-up of haematological malignancy was available in 365 patients who were followed for a mean time of 8.06 years (Supplementary Fig. S1, available at *Rheumatology* online). Forty-seven (12.9%) patients died, mainly due to malignancy progression ($n = 20$, 51%) and infections ($n = 12$, 31%). Fig. 2A shows the Kaplan–Meier curve of the cumulative survival free of death. The 1-year, 2-year and 5-year survival rates were 93.2%, 90.0% and 86.5%, respectively.

Specific substudies

Lymphoma subtypes

Table 2 summarizes the differences between the main lymphoma subtypes (MALT lymphoma, nodal MZL, DLBCL, CLL/SLL and FL). There were significant differences with respect to the age at diagnosis (younger in MALT, older in CL/SLL, $P = 0.002$), pattern of clinical

FIG. 2 Disease-specific survival among patients with malignancy



(**A**) Kaplan–Meier survival curve being free of death in the overall cohort. (**B**) Kaplan–Meier survival curve according to the five main subtypes of mature B-cell haematological malignancy. (**C**) Kaplan–Meier survival curve according to salivary *vs* extrasalivary involvement. (**D**) Kaplan–Meier survival curve according to timing presentation.

presentation (glandular enlargement in MALT lymphoma, peripheral lymphadenopathy in nodal MZL and FL, constitutional symptoms in DLBCL, incidental diagnosis in CLL/SLL), therapeutic response (higher in MALT lymphoma, lower in DLBCL) and survival (better in MALT lymphoma, nodal MZL and FL, worse in DLBCL). Fig. 2B shows the Kaplan–Meier curves of the cumulative survival among patients with the main lymphoma subtypes.

Salivary vs extrasalivary lymphoma

Patients classified as having lymphoma arising in salivary glands were diagnosed at a younger age, had a higher frequency of MALT lymphoma and a lower frequency of DLBCL, a higher rate of CR and a lower mortality rate in comparison with patients with extrasalivary lymphoma (Table 3). Fig. 2C shows the Kaplan–Meier curves of the cumulative survival of patients with salivary and extrasalivary lymphoma.

Haematological malignancy preceding SS diagnosis

In 43 (10%) patients, haematological malignancy was diagnosed at least one year before the diagnosis of SS. These patients were diagnosed with the haematological malignancy at an older age, were less frequently diagnosed with a B-cell malignancy, had a higher rate of CR and a lower mortality rate in comparison with patients where the malignancy was diagnosed concomitantly or after SS diagnosis (Table 4). Fig. 2D shows the Kaplan–Meier curves of the cumulative survival of patients diagnosed with malignancy before or after the SS diagnosis.

Systemic SS activity

The mean ESSDAI score was similar among the lymphoma subgroups (Table 2), while for the organ-specific domains, patients diagnosed with MALT are those with the higher rate of activity in the glandular domain while those diagnosed with DLBCL had the higher rate of activity in the constitutional domain. There were 31 patients who had systemic activity at the time of malignancy in other clinical ESSDAI domains including the

TABLE 2 Comparison of the main mature B-cell lymphoma subtypes

Variables	Mature B cells (main subtypes)					
	MALT[a] Lymphoma ($n = 197$)	Nodal MZL[b] ($n = 29$)	DLBCL[c] ($n = 67$)	CL/SLL[d] ($n = 19$)	FL[e] ($n = 17$)	*P*
Epidemiological features						
Gender (female)	171 (86.8)	26 (89.7)	56 (93.6)	18 (94.7)	13 (76.5)	0.513
Age (mean, years)	49.3 (13.0)	54.3 (14.3)	53.3 (13.8)	59.9 (15.1)	56.2 (12.1)	0.002
Time of follow-up after lymphoma diagnosis (years)	8.7 (6.6)	6.8 (5.0)	6.3 (5.7)	6.9 (5.6)	13 (8.4)	0.004
Timing of diagnosis						
Lymphoma diagnosed concomitant/after SS	185 (93.9)	28 (96.6)	64 (95.5)	15 (78.9)	14 (82.4)	0.037
Clinical features at presentation						
Constitutional symptoms	44/173 (25.4)	10 (34.5)	33/62 (53.2)	2/15 (13.3)	7/16 (43.8)	0.001
Glandular enlargement	137/174 (78.7)	10 (34.5)	10/62 (16.1)	2/15 (13.3)	3/16 (18.8)	<0.001
Peripheral lymphadenopathy	22/173 (12.7)	15 (51.7)	32/62 (51.6)	3/15 (20.0)	8/16 (50.0)	<0.001
Incidental diagnosis	2/174 (1.1)	0 0	1/62 (1.6)	7/15 (46.7)	0/16 0	<0.001
Outcomes						
Complete response	136/148 (91.9)	17/20 (85.0)	36/52 (69.2)	1/3 (33.3)	6/9 (66.7)	<0.001
Relapse	45/146 (30.8)	11/20 (55.0)	14/46 (30.4)	1/2 (50.0)	5/9 (55.6)	0.140
Death	7/181 (3.9)	3/26 (11.5)	17/57 (29.8)	2/16 (12.5)	0/13 0	<0.001
Total ESSDAI[f]	19.0 (5.5)	18.0 (5.6)	18.1 (6.2)	15.3 (4.3)	15.3 (4.3)	0.061
ESSDAI domains[g]	$n = 185$	$n = 28$	$n = 64$	$n = 15$	$n = 14$	
Constitutional	27 (14.6)	10 (35.7)	27 (42.2)	2 (13.3)	4 (28.6)	<0.001
Lymphadenopathy	185 (100)	28 (100)	64 (100)	15 (100)	14 (100)	1.000
Glandular	137 (78.7)	9 (32.1)	13 (20.3)	4 (26.7)	3 (21.4)	<0.001
Articular	29 (15.7)	5 (17.9)	5 (7.8)	0 0	3 (21.4)	0.201
Cutaneous	15 (8.1)	5 (17.9)	4 (6.2)	1 (6.7)	0 0	0.276
Pulmonary	3 (1.6)	1 (3.6)	2 (3.1)	0 0	0 0	0.823
Renal	0 0	0 0	0 0	0 0	0 0	1.000
Muscular	0 0	0 0	0 0	0 0	0 0	1.000
PNS	15 (8.1)	0 0	4 (6.2)	0 0	0 0	0.296
Central nervous system	0 0	0 0	0 0	0 0	0 0	1.000
Haematological	48 (25.9)	7 (25)	19 (29.7)	2 (13.3)	5 (35.7)	0.673
Biological	108 (58.4)	14 (50)	26 (40.6)	4 (26.7)	5 (35.7)	0.020

[a]MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. [b]MZL: marginal zone lymphoma. [c]DLBCL: diffuse large B-cell lymphoma. [d]CLL/SLL: chronic lymphocytic leukaemia/small lymphocytic lymphoma. [e]FL: follicular cell lymphoma. [f]Disease activity at the time of lymphoma diagnosis. Forty-three patients with neoplasia before SS diagnosis were excluded ($n = 371$). [g]Level of activity is recorded as no *vs* any type of activity (low/moderate/high) in the analysis.

cutaneous ($n = 21$), neurological ($n = 15$), pulmonary ($n = 4$) and renal ($n = 2$) domains. In these patients, systemic activity was completely resolved in 21 (68%), partially resolved in six (19%) and non-resolved in four (13%) patients after receiving specific treatment for malignancy. The total mean ESSDAI scores were stratified according to the therapeutic response achieved (19.1 [6.3] in patients with CR, 18.1 [5.1] in those with PR and 17.8 [6.7] in non-responders, $P = 0.47$) and the survival (16.8 [5.2] in patients who died *vs* 18.4 [5.9] in survivors, unadjusted *P*-value of 0.052, adjusted according to the type of lymphoma and Ann Arbor classification, $P = 0.122$).

Risk factors of haematological malignancy

The main baseline features identified at the time of SS diagnosis as the strongest risk factors associated with the development of haematological malignancy ($P < 0.001$) included abnormal results in the diagnostic oral tests, immunological parameters (ANA, RF, anti-Ro, anti-La, monoclonal cryoglobulins, low C3 and low C4 values) and a high baseline systemic activity both for total (ESSDAI and DAS) and organ-specific (constitutional, lymphadenopathy, glandular, haematological and biological domains) scores in comparison with the age, sex and disease duration-matched controls without haematological malignancy (Table 5).

Discussion

The SIR for overall haematologic malignancy is 11-fold higher in primary SS than in the general population [15]. Specifically, primary SS patients have an increased risk

Table 3 Comparison of salivary *vs* extrasalivary gland lymphomas

Variables	Salivary glands *n* = 168	Extra-salivary sites *n* = 77	*P*	Unadjusted OR 95% CI	Adjusted OR 95% CI
Epidemiological features					
Gender (female)	144 (85.7)	67 (87.0)	0.941	0.90 [0.39, 1.93]	0.86 [0.37, 1.87]
Age (mean, years)	48.5 (12.4)	53.0 (13.9)	0.016	0.97 [0.95, 0.99]	0.97 [0.95, 0.99]
Time of follow-up after lymphoma diagnosis (years)	8.1 (5.7)	8.9 (8.1)	0.467	0.98 [0.94, 1.03]	0.98 [0.93, 1.02]
Timing of diagnosis. Lymphoma concurrent/after SS diagnosis	158 (94.0)	66 (85.7)	0.055	2.63 [1.06, 6.61]	2.27 [0.90, 5.79]
Clinical features					
Constitutional symptoms	33/155 (21.3)	20/70 (28.6)	0.307	0.68 [0.36, 1.30]	0.67 [0.35, 1.30]
Peripheral lymphadenopathy	17/155 (11.0)	8/70 (11.4)	1,000	0.95 [0.40, 2.45]	0.88 [0.36, 2.28]
Incidental diagnosis	0/155 0	3/70 (4.3)	0.049	—	—
Mature B cell types					
MALT lymphoma[a]	144 (85.7)	34 (44.2)	<0.001	7.59 [4.11, 14.36]	7.45 [3.99, 14.29]
Nodal MZL[b]	9 (5.4)	7 (9.1)	0.412	0.57 [0.20, 1.64]	0.62 [0.22, 1.81]
DLBCL[c]	6 (3.6)	21 (27.3)	<0.001	0.10 [0.03, 0.24]	0.10 [0.03, 0.25]
CLL/SLL[d]	2 (1.2)	3 (3.9)	0.366	0.30 [0.04, 1.83]	0.28 [0.03, 1.78]
FL[e]	3 (1.8)	2 (2.6)	1,000	0.68 [0.11, 5.26]	0.60 [0.09, 4.86]
Outcomes					
Complete response	118/126 (93.7)	46/62 (74.2)	<0.001	5.13 [2.11, 13.43]	4.28 [1.71, 11.42]
Relapse	38/125 (30.4)	21/57 (36.8)	0.490	0.75 [0.39, 1.46]	0.79 [0.41, 1.57]
Death	4/154 (2.6)	12/66 (18.2)	<0.001	0.12 [0.03, 0.36]	0.15 [0.04, 0.46]

[a]MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. [b]MZL: marginal zone lymphoma. [c]DLBCL: diffuse large B-cell lymphoma. [d]CLL/SLL: chronic lymphocytic leukaemia/small lymphocytic lymphoma. [e]FL: follicular cell lymphoma.

Table 4 Comparison of hematological malignancy according to timing presentation

Variables	Timing		*P*	Unadjusted OR [95% CI]	Adjusted OR [f] [95% CI]
	Prior to SS diagnosis (*n* = 43)	Concurrent/after SS diagnosis (*n* = 371)			
Epidemiological features					
Gender (female)	41 (95.3)	314 (84.6)	0.095	3.72 [1.1, 23.23]	3.92 [1.15, 24.65]
Age (mean, years)	60.0 (12.8)	51.5 (13.6)	<0.001	1.05 [1.02, 1.08]	1.05 [1.02, 1.08]
Time of follow-up (years)	15.5 (8.8)	7.1 (5.8)	<0.001	1.16 [1.11, 1.21]	1.20 [1.13, 1.27]
Clinical features					
Constitutional symptoms	6/33 (18.2)	120/337 (35.6)	0.068	0.40 [0.15, 0.94]	0.39 [0.14, 0.93]
Glandular enlargement	11/33 (33.3)	157/338 (46.4)	0.207	0.58 [0.26, 1.20]	0.80 [0.35, 1.76]
Peripheral lymphadenopathy	9/33 (27.3)	100/337 (29.7)	0.929	0.89 [0.38, 1.92]	0.79 [0.33, 1.75]
Incidental diagnosis	7/33 (21.2)	25/338 (7.4)	0.018	3.37 [1.25, 8.21]	2.47 [0.88, 6.24]
WHO main groups (B)	34 (79.1)	342 (92.2)	0.011	0.32 [0.14, 0.77]	0.35 [0.15, 0.88]
Mature B cell types					
MALT lymphoma[a]	12 (27.9)	185 (49.9)	0.010	0.39 [0.19, 0.76]	0.48 [0.23, 0.97]
Nodal MZL[b]	1 (2.3)	28 (7.5)	0.340	0.29 [0.02, 1.42]	0.25 [0.01, 1.27]
DLBCL[c]	3 (7.0)	64 (17.3)	0.130	0.36 [0.09, 1.03]	0.33 [0.08, 0.97]
CLL/SLL[d]	4 (9.3)	15 (4.0)	0.240	2.43 [0.67, 7.10]	1.61 [0.42, 4.97]
FL[e]	3 (7.0)	14 (3.8)	0.551	1.91 [0.43, 6.17]	1.89 [0.41, 6.37]
Outcomes					
Complete response	27/29 (93.1)	198/252 (78.6)	0.107	3.68 [1.06, 23.28]	4.48 [1.22, 29.03]
Relapse	11/29 (37.9)	79/234 (33.8)	0.811	1.20 [0.53, 2.63]	1.13 [0.48, 2.53]
Death	1/40 (2.5)	46/325 (14.2)	0.068	0.16 [0.01, 0.74]	0.12 [0.01, 0.57]

[a]MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. [b]MZL: marginal zone lymphoma. [c]DLBCL: diffuse large B-cell lymphoma. [d]CLL/SLL: chronic lymphocytic leukaemia/small lymphocytic lymphoma. [e]FL: Follicular cell lymphoma. [f]Adjusted OR by sex and age at diagnosis.

TABLE 5 Comparison of clinical and serological features among patients with and without haematological malignancy

Variables	Patients with haematological malignancy[a] (*n* = 371)	Age-sex matched controls [b] (*n* = 742)	*P*
Age at diagnosis of SS (mean)	52.1 (13.5)	52.0 (13.6)	0.965
Sex (woman)	315 (84.9)	630 (84.9)	1,000
Disease duration, years	11.7 (7.7)	11.3 (7.6)	0.897
Ethnicity			0.258
White	331 (89.2)	631/740 (85.3)	
Hispanic	20 (5.4)	43/740 (5.8)	
Black African-American	5 (1.3)	12/740 (1.6)	
Asian	15 (4)	52/740 (7)	
Others	0 0	2/740 (0.3)	
Dry eye	351 (94.6)	690 (93)	0.366
Dry mouth	363 (97.8)	689 (92.9)	0.001
Altered ocular tests	274/298 (91.9)	539/623 (86.5)	0.022
Abnormal oral tests	254/271 (93.7)	442/549 (80.5)	<0.001
Positive salivary gland biopsy	231/252 (91.7)	488/547 (89.2)	0.344
Antinuclear antibodies+	326/363 (89.8)	612/721 (84.9)	0.032
Rheumatoid factor+	210/339 (61.9)	338/686 (49.3)	<0.001
Anti-Ro/SS-A+	301/366 (82.2)	525/729 (72)	<0.001
Anti-La/SS-B+	201/365 (55.1)	319/723 (44.1)	0.001
Cryoglobulins+	68/239 (28.5)	40/405 (9.9)	<0.001
Low C3 levels (<0.82 g/L)	79/301 (26.2)	87/633 (13.7)	<0.001
Low C4 levels (<0.11 g/L)	87/294 (29.6)	93/633 (14.7)	<0.001
Baseline ESSDAI	13.2 (12.6)	7.0 (8.3)	<0.001
Baseline DAS			<0.001
Low	98/323 (30.3)	358/707 (50.6)	
Moderate	96/323 (29.7)	234/707 (33.1)	
High	129/323 (39.9)	115/707 (16.3)	
ESSDAI domains[c]			
Constitutional	72/336 (21.4)	77/707 (10.9)	<0.001
Lymphadenopathy	148/336 (44)	75/707 (10.6)	<0.001
Glandular	153/336 (45.5)	156/707 (22.1)	<0.001
Articular	116/336 (34.5)	305/707 (43.1)	0.010
Cutaneous	47/336 (14)	83/707 (11.7)	0.354
Pulmonary	42/336 (12.5)	81/707 (11.5)	0.700
Renal	17/336 (5.1)	29/707 (4.1)	0.587
Muscular	11/336 (3.3)	18/707 (2.5)	0.641
PNS	38/336 (11.3)	54/707 (7.6)	0.066
CNS	5/336 (1.5)	23/707 (3.3)	0.149
Haematological	134/329 (40.7)	168/690 (24.3)	<0.001
Biological	233/325 (71.7)	352/646 (54.5)	<0.001

[a]Level of activity is recoded as no *vs* any type of activity (low/moderate/high) in the analysis. [b]Age, sex and disease duration matched SS patients without lymphoma. [c]43 patients with neoplasia before SS diagnosis were excluded (*n* = 371).

of lymphoma [28–31] that is driven by individual epidemiological, clinical, immunological and histological factors [6, 7, 11, 12, 14, 15, 17, 32–34]. We present the largest reported cohort of primary SS patients complicated with haematological malignancies, 91% of which are B-cell lymphomas, a similar rate as reported in smaller studies [6, 9, 16, 20] (Supplementary Table S1, available at *Rheumatology* online). Mature T malignancy accounted for only 2% of haematological malignancies, a figure substantially lower than in the general population (10–15%) [35], and which highlights the overwhelming predominance of B-cell malignancy in SS.

In the general population, the most frequent lymphoma subtypes are DLBCL (21%), CLL/SLL (15%), FL (9%) and MZL (3%) [36]. In contrast, in our patients, the frequencies were 16% for DLBCL, 5% for CLL/SLL, 4% for FL and 55% for MZL (Supplementary Table S3, available at *Rheumatology* online). An international consortium estimated a 30-fold increased risk for MZL, a 9-fold increased risk for DBCL and a 4-fold increased risk for FL in primary SS [34]. The predominance of MZL in primary SS (overwhelmingly represented by the MALT subtype) is not surprising considering that it is a group of low-grade (indolent) extranodal B-cell lymphoma that

arises in areas of preexisting chronic lymphoid proliferation in mucosal sites [37]. All previous studies in primary SS have reported a similar distribution (MALT as the most frequent subtype, DLBCL the second most frequent) (Supplementary Table S1, available at *Rheumatology* online).

A key objective of our study was to characterize the different B-cell lymphoma subtypes. Previously, only a few studies have reported data comparing MALT lymphoma and DLBCL [14, 20, 38, 39]. We observed substantial differences in the ratio of affected women (18:1 for CLL/SLL, around only 3:1 for FL) and in the age at malignancy diagnosis (the youngest in MALT lymphoma and the oldest in CLL/SLL patients). There was also a differential clinical presentation of malignancy, consisting of glandular enlargement in MALT lymphoma, peripheral lymphadenopathy in nodal MZL and FL, constitutional symptoms in DLBCL, and incidental diagnosis in CLL/SLL. The therapeutic response and the survival rates were also different (higher in MALT lymphoma, lower in DLBCL).

We confirmed salivary glands as the major primary site of haematologic malignancy in primary SS (around 40% of cases), supporting a link with the pathogenesis of the disease [5]. The distribution of the different B-cell malignancy subtypes in salivary gland in primary SS was also clearly different from the general population given the predominant role of MALT lymphoma, in 85% of our cases. In contrast, in non-SS population, the proportion of each lymphoma subgroup in the parotid gland is similar (about 23–27%) [40].The reason for the overwhelming involvement of the parotid glands over the lachrymal glands is unknown. One possibility might be a change in the oral microbiota due to the chronic autoimmune damage or a higher amount of immune complexes in saliva.

We also reported lymphomas in other extranodal sites, including the digestive system in 7.4% (mainly stomach), ENT sites in 3.2% (mainly palate) and the respiratory system in 2.7% (mainly lung), a different scenario to that reported in non-SS population, in which stomach (30–40%) and the skin [37] are the main sites. The higher mortality rate of patients with extra-salivary lymphoma could be attributed to the predominance of DLBCL, which has the highest mortality rate among the different lymphoma subtypes in our SS cohort (30%), although this rate is similar to that reported in middle-aged persons with DLBCL unrelated to SS (12–39%) [41].

Haematological malignancy was reported at least one year before the SS diagnosis in 10% of our patients. One might think that these are patients in whom SS was in a quiescent stage for years until the neoplasm appeared, but their mean age is almost 10 years older than the age at which the malignancy was diagnosed in patients already diagnosed with SS. Although this group was less frequently diagnosed with B-cell malignancy; MALT lymphoma remained the most prevalent subtype (Supplementary Fig. S3, available at *Rheumatology* online). And it is probable that their lower mortality may be underestimated, as some patients may have died before the SS diagnosis. Among the Swedish patient register, 18 of 107 lymphoma cases were diagnosed before or within 6 months of primary SS diagnosis. These patients were more often men, had lymphadenopathy and salivary gland MALT lymphoma [19].

Regarding the association between systemic activity (ESSDAI scores) and lymphoma in primary SS patients, we found an expected correlation with some specific lymphoma subtypes (higher constitutional activity in DLBCL and higher glandular activity in MALT lymphoma), demonstrating the great overlap between the key lymphoma-related clinical and laboratory features and most of the ESSDAI domains. The main example is the maximum score achieved in the lymphadenopathy domain by all patients diagnosed with malignancy (score of 12), followed by the evident overlap in most of the other ESSDAI domains including constitutional (fever, weight loss), glandular (parotid enlargement), haematological (cytopenias) and biological (hypergammaglobulinemia, monoclonal bands). Therefore, in >90% of our cases, lymphoma features contributed to 75–100% of the total ESSDAI score measured at the time of lymphoma diagnosis. In addition, there is an additional therapeutic confounder effect because the key therapeutic drugs used for treating lymphoma (corticosteroids, cyclophosphamide, rituximab) are agents that are also extremely effective against systemic disease. In fact, we found that pre-therapeutic ESSDAI score was not a predictive factor for either a better lymphoma therapeutic response or for a better survival.

Some limitations must be mentioned. First, because of our retrospective design, we did not have complete information in all patients, and the diagnostic approach and treatment options may have changed over the years. Nonetheless, the quality of our information was carefully recorded and provided by expert centres. Second, 155 of the patients in our cohort have been included in previous publications [8, 12, 13, 15]. Third, the predominant presence of European patients could limit the external validity of our study. Fourth, a survival bias cannot be discarded in order to explain the differences in death rates between those diagnosed before and after a diagnosis of SS. And finally, because the participant centres are mainly tertiary university centres, the magnitude of the selection bias may vary between countries.

Summing up, this study is the largest on haematological malignancy in patients with primary SS. The specific pathogenesis of this disease may explain the very specific profile of haematological malignancies, overwhelmingly dominated by B-cell origin, especially MALT, with the salivary glands being the primary site of involvement. We also confirmed the predictive role of immunological parameters and systemic disease reported in previous smaller studies [6, 7, 11, 12, 14, 15, 17, 32–34], suggesting that an enhanced baseline polyclonal Ig expansion may facilitate the development of monoclonal processes conferring a higher risk of developing haematological malignancies, as was reported by previous

smaller studies [11, 14, 15, 42]. The histopathological scenario was linked to the overall good prognosis with a 5-year survival rate higher than 80%. It is important to highlight that histopathological findings in primary SS expand well beyond parotid MALT lymphoma. In addition, one in ten primary SS patients will have a haematological malignancy diagnosed at least one year before the SS diagnosis; therefore, haematologists should keep this in mind to recognize coexisting SS. Our findings converge in one direction: to ensure the mandatory and bidirectional multidisciplinary follow-up of both patients with primary SS and those with haematological malignancy.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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