The clinical phenotype of primary Sjögren's syndrome patients with lymphadenopathy

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Abstract

Objective

Previous cohort studies have shown that around 10% of patients with primary Sjögren's syndrome (pSS) develop lymphadenopathy during their disease course. However, no studies have described their clinical phenotype. The present study aims to describe the clinical manifestations and laboratory findings of pSS patients presenting long-standing lymphadenopathy.

Methods

From a total of 1234 consecutive pSS patients fulfilling the 2016 ACR-EULAR criteria, those with stable lymphadenopathy unrelated to lymphoma were identified (lymphadenopathy group). Their clinical data were collected and compared with 2 control groups: a) the remaining unmatched pSS patients without lymphadenopathy (unmatched non-lymphadenopathy group) and b) pSS patients without lymphadenopathy matched for age, sex, and disease duration, in an approximately 1:1 ratio (matched non-lymphadenopathy group).

Results

One hundred and sixty-five (13.37%) patients presented persistent, stable lymphadenopathy. They were characterised by younger age at both pSS onset and diagnosis, and by shorter disease duration. Compared to the unmatched non-lymphadenopathy group, patients with lymphadenopathy had more frequently salivary gland enlargement ($p<0.001$), higher focus score at first salivary gland biopsy ($p=0.017$), palpable purpura ($p<0.001$), peripheral nervous system involvement ($p=0.012$), glomerulonephritis ($p<0.001$), and leukopenia ($p<0.001$), while the results of the matched comparison were similar. Regarding the serological profile, the comparison with the unmatched group demonstrated higher frequency of ANA ($p=0.013$), anti-Ro/SSA ($p=0.001$), and anti-La/SSB ($p<0.001$) positivity for the lymphadenopathy group, while in the matched comparison only higher rates of anti-Ro/SSA positivity ($p=0.002$) remained statistically significant.

Conclusion

pSS patients presenting non-lymphoma related stable lymphadenopathy constitute a subgroup of younger individuals with B-cell hyperactivation.

Key words

Sjögren's syndrome, lymphadenopathy, autoimmunity, lymphoid hyperplasia

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Introduction

Primary Sjögren's Syndrome (pSS) is a chronic systemic autoimmune disease with a diverse clinical spectrum, ranging from mild, benign exocrinopathy to full-blown systemic disease (1). The central role of B-cells in the pathogenesis of the disease is indicated by the plethora of autoantibodies, the frequent presence of hypergammaglobulinemia and the increased risk for B-cell lymphoma development (2, 3), predominantly mucosa-associated lymphoid tissue (MALT) lymphoma with a rather favourable prognosis (4). Approximately 10% of pSS patients display clinically apparent lymphadenopathy (5). This clinical manifestation may be either related to concurrent lymphoma development or may constitute a benign reactive lymphoid tissue hyperplasia in the setting of autoimmunity. Chronic antigenic stimulation drives the lymphoid infiltration in the salivary glands (SGs) of pSS patients, with a more prominent B-cell component characterizing the severe lesions (6); in accordance the presence of germinal centre (GC)-like structures (GCLS) within SGs has been proposed as lymphoma predictor and has been associated with systemic disease activity (7-9). Beyond the studied histopathology of lymph node enlargement in lymphoma cases, there is a paucity of data regarding the histology and the clinical significance of the "non-malignant" enlarged lymph nodes in the context of pSS *per se*. However, the reactive lymphoid hyperplasia with increased lymphoid follicles in the lymph nodes of pSS patients (10, 11) points out chronic antigenic stimulation, that drives SG lymphoid expansion, as the common denominator between GCLS and pSS related "non-malignant" lymphadenopathy. The European League Against Rheumatism (EULAR) SS disease activity index (ESSDAI) has incorporated the lymphadenopathy domain as one of the parameters contributing to the overall disease activity (12). Reports on the subgroup of pSS patients with lymphadenopathy unrelated to lymphoma are lacking. Therefore, in the present study we describe the clinical features and the laboratory profile of this subset of pSS patients and explore possible differences in comparison to pSS patients without lymph node enlargement.

Patients and methods

After excluding patients with lymphadenopathy secondary to infections, malignancy including non-Hodgkin lymphomas (NHLs), and non-available data, the medical records of 1234 consecutive pSS patients from Greece and Italy were reviewed. All patients fulfilled the 2016 American College of Rheumatology (ACR)/EULAR criteria. Patients with lymphadenopathy were identified according to the relevant ESSDAI domain (12), as follows: a) lymph node enlargement with a diameter of ≥1cm in any nodal region or ≥2cm in the inguinal region on clinical examination, b) lymph node enlargement with a maximal diameter of ≥1cm in any nodal region or ≥2cm in the inguinal region, for patients with available ultrasound or CT, c) exclusion of infection or cancer, d) persistence of lymph node enlargement for at least 6 months, d) for patients with lymph node enlargement and clinical suspicion for lymphoma, histological examination of the affected node to exclude an underlying active lymphoproliferative disorder. Cumulative, clinical, laboratory, immunologic and histologic data were collected from all participants. pSS patients with lymphadenopathy were compared with 2 control groups: a) unmatched pSS patients without lymphadenopathy (unmatched non-lymphadenopathy group) (n=1069), and b) pSS patients without lymphadenopathy matched for age, sex, and disease duration, in an approximately 1:1 ratio (matched non-lymphadenopathy group) (n= 201). Statistical analysis for categorical data was performed by χ^2 test, with Yates correction or Fisher exact when cell counts involved <5 patients/items, while for numerical data the t test or Mann-Whitney methods were used, after implementing the Shapiro-Wilk normality test. A p value <0.05 was considered statistically significant.

Results

Of the 1234 pSS patients, 165 (13.37 %) developed stable lymphadenopathy dur-

ing the disease course. More than 90% of lymphadenopathy cases involved the cervical region, while the rest included the axillaries and the supraclavicular areas. Females prevailed in both the lymphadenopathy (95.7%) and the non-lymphadenopathy unmatched group (95.5%). The lymphadenopathy group was characterised by a younger age at pSS diagnosis (median 46 years old, range: 10-81 years) compared to the non-lymphadenopathy unmatched group (median 53 years old, range: 11-85 years) ($p<0.001$), as well as by a younger median age at disease onset [median 43 years old (range: 7–76 years) *vs*. 49 years old (range: 5–84 years), $p=0.001$]. Moreover, pSS patients with lymphadenopathy demonstrated shorter disease duration (median 7 years *vs*. 10 years, $p=0.008$), with no statistically significant differences in the reported symptoms of mouth and ocular dryness compared to their non-lymphadenopathy unmatched counterparts. Lymphadenopathy pSS patients presented more frequently with SG enlargement (SGE) (39% *vs*. 21.6%, $p<0.001$), palpable purpura (14.5% *vs*. 5.7%, $p<0.001$), peripheral nervous system (PNS) involvement (4.9% *vs*. 1.5%, $p=0.012$), glomerulonephritis (4.8% *vs*. 0.5%, $p<0.001$) and higher focus score (FS) at first SG biopsy (median 1.9 *vs*. 1.3, $p=0.01$) compared to the unmatched pSS controls. The serological profile of the lymphadenopathy group was characterised by higher frequencies of antinuclear antibodies (ANA) (95.7% *vs*. 89.2%, $p=0.013$), anti-Ro/SSA (87.2% *vs*. 75.7%, $p=0.001$) and anti-La/SSB (47.2% *vs*. 32.9%, $p=0.0004$) positivity. Regarding the haematological parameters, pSS patients with lymphadenopathy displayed higher prevalence of leukopenia (21.2% *vs*. 7.9%, $p<0.001$), neutropenia (12.4% *vs*. 6.8%, $p=0.02$) and lymphopenia (20.2% *vs*. 8.3%, $p<0.001$) compared to the non-lymphadenopathy unmatched group (Table I).

The comparison between the lymphadenopathy group and their matched non-lymphadenopathy control group, showed a median age at pSS diagnosis of 46 years old for both groups (range: 10-81 and 15-80 years old, respectively), while the median disease duration from pSS diagnosis to last follow-up was 4 (range 0–27 years) and 5 years (range 0-30 years), respectively. Patients with lymphadenopathy presented more frequently with SGE (39% *vs*. 20%, $p=0.0001$), palpable purpura (14% *vs*. 6%, $p=0.01$), PNS vasculitis (5% *vs*. 0.5%, $p=0.01$), glomerulonephritis (4.8% *vs*. 0.5%, $p=0.01$), and higher FS at first SG biopsy (median 1.91 *vs*. 1.19, $p=0.004$) compared to their matched non-lymphadenopathy controls. No statistically significant difference was found between the 2 groups regarding ANA and anti-La/SSB positivity, but the lymphadenopathy pSS patients had still higher frequencies of anti-Ro/SSA (87% *vs*. 74%, $p=0.002$) than the matched controls. Regarding the haematological parameters, leukopenia (21.2% *vs*. 7.5%,

Table I. Comparison of clinical and laboratory features of all pSS patients with (lymphadenopathy group) and without lymphadenopathy (unmatched non-lymphadenopathy group).

	Lymphadenopathy group, %, n=165	Unmatched non-lymphadenopathy group, %, n=1069	*p*-value
Demographics			
Female sex	95.7% (158/165)	95.5% (1021/1069)	0.95
Median age at pSS diagnosis (years)	46	53	**<0.001**
Median age at pSS onset (years)	43	49	**0.001**
Median disease duration from pSS diagnosis to last follow up (years)	5	5	0.9
Median disease duration from pSS onset to last follow up (years)	7	10	**0.008**
Glandular and non-specific manifestations			
Dry mouth-subjective	92.1% (152/165)	93.1% (991/1064)	0.75
Dry eyes-subjective	95.1% (157/165)	93% (994/1068)	0.4
SGE	39% (64/164)	21.6% (229/1060)	**<0.001**
FS 1st biopsy	1.9 1.3	**0.017**	
Raynaud's phenomenon	18.2% (29/159)	24.3% (251/1029)	0.1
Arthralgias-myalgias	63% (104/165)	63.6% (677/1063)	0.93
Splenomegaly	1.8% (1/54)	0.1% (1/717)	0.13
Extraepithelial manifestations			
Glomerulonephritis	4.8% (8/164)	0.5% (6/1064)	**<0.001**
Autoimmune hepatitis	0.6% (1/159)	0.8% (7/798)	1
Peripheral nervous disease	4.9% (8/163)	1.5% (17/1065)	**0.012**
Palpable purpura	14.5% (24/165)	5.7% (61/1069)	**<0.001**
Periepithelial manifestations			
Interstitial renal disease	1.8% (3/163)	1.9% (21/1051)	1
Primary biliary cholangitis	1.8% (3/165)	2% (22/1069)	1
Sclerosing cholangitis	0% (0/159)	1.2% (10/798)	0.38
Serology			
ANA+	95.7% (158/165)	89.2% (932/1044)	**0.013**
RF+	59.3% (95/160)	51.8% (517/997)	0.09
Anti-Ro	87.2% (144/165)	75.7% (792/1046)	**0.001**
Anti-La	47.2% (78/165)	32.9% (340/1033)	**<0.001**
Low C4	27.8% (44/158)	27% (273/1011)	0.89
Cryoglobulinaemia	6.9% (10/144)	4.9% (30/605)	0.45
Complete blood count			
Leukopenia	21.2% (35/165)	7.9% (85/1064)	**<0.001**
Neutropenia	12.4% (19/153)	6.8% (61/888)	0.02
Lymphopenia	20.2% (31/153)	8.3% (74/882)	**<0.001**

SGE: salivary gland enlargement; FS: focus score.

$p<0.001$) and lymphopenia (20.2% *vs*. 8.2%, $p=0.004$) were more often observed in the lymphadenopathy group compared to their matched controls (Table II).

Table II. Comparison of clinical and laboratory features of all pSS patients with (lymphadenopathy group) and without lymphadenopathy (matched non-lymphadenopathy group).

	Lymphadenopathy group, %, n=165	Matched non-lymphadenopathy group, %, n=201	*p*-value
Demographics			
Female sex	96% (158/165)	96% (194/201)	0.91
Median age at pSS diagnosis (years)	46	46	0.74
Median age at pSS onset (years)	43	42	0.57
Median disease duration from pSS diagnosis to last follow up (years)	5	4	0.65
Median disease duration from pSS onset to last follow up (years)	7	9	0.09
Glandular and non-specific manifestations			
Dry mouth-subjective	92% (152/165)	93% (187/200)	0.76
Dry eyes-subjective	95% (157/165)	91% (182/200)	0.18
SGE	39% (64/164)	20% (40/200)	**<0.001**
FS 1st biopsy	1.91	1.19	**0.004**
Raynaud's phenomenon	18% (19/159)	25% (49/192)	0.13
Arthralgias-myalgias	63% (104/165)	65% (132/201)	0.67
Splenomegaly	2% (1/54)	0% (0/144)	0.27
Extraepithelial manifestations			
Glomerulonephritis	4.8% (8/164)	0.5% (1/200)	**0.01**
Autoimmune hepatitis	0.6% (1/159)	0% (0/140)	1
Peripheral nervous disease	5% (8/163)	0.5% (1/199)	**0.01**
Palpable purpura	14% (24/165)	6% (13/201)	**0.01**
Peripepithelial manifestations			
Interstitial renal disease	1.8% (3/163)	2% (4/197)	1
Primary biliary cholangitis	1.8% (3/165)	2.9% (6/201)	0.52
Sclerosing cholangitis	0% (0/159)	1.4% (2/140)	0.21
Serology			
ANA+	95% (158/165)	90% (176/195)	0.07
RF+	59% (95/160)	50% (93/186)	0.1
Anti-Ro	87% (144/165)	74% (146/197)	**0.002**
Anti-La	47% (78/165)	37% (73/87)	0.06
Low C4	27% (44/158)	24% (46/191)	0.49
Cryoglobulinaemia	6.9% (10/144)	3.8% (4/105)	0.4
Complete blood count			
Leukopenia	21.2% (35/165)	7.5% (15/199)	**<0.001**
Neutropenia	12.4% (19/153)	5.6% (9/159)	0.05
Lymphopenia	20.2% (31/153)	8.2% (13/157)	**0.004**

SGE: salivary gland enlargement; FS: focus score.

Discussion

Autoimmunity associated lymphadenopathy shows marked clinical and histological diversity. The majority of published histopathological studies include cases related to rheumatoid arthritis and systemic lupus erythematosus, while reports on pSS lymphadenopathy, unrelated to lymphoma, are scarcer. However, it seems that the common histopathological features of paracortical hyperplasia and lymphoid follicle expansion, overall termed reactive follicular hyperplasia, are shared in systemic autoimmunity (10, 13, 14). This follicular pattern is driven by a humoral immune reaction after persistent antigenic stimulation and subsequent proliferation of B-cells. A study by McCurley *et al*., investigating the lymph node histopathology in the setting of pSS, reported that the subset of pSS patients with lymphadenopathy may have either B-cell lymphoma or reactive follicular hyperplasia (11). In this context and given that pSS patients are at high risk for B-cell lymphomas, it appears of major clinical significance to study the phenotype of pSS patients with non-malignant lymphadenopathy attributed to the pathogenetic mechanisms of pSS itself and not to an active lymphoproliferative disorder. As reviewed by Cafaro *et al*. the definition of distinct disease phenotypes enables us to risk-stratify pSS patients and to predict different outcomes (15). In general, patient stratification based on clinical phenotyping is an easy strategy to identify distinct patients' subgroups, to reveal disease endotypes, to optimise follow-up approaches and to tailor possible therapeutic interventions.

Our study, gathers some unique points, worthy to be mentioned: i) well characterised pSS patients with strictly defined lymphadenopathy by excluding lymphoma cases or other potential causes of lymph node enlargement; ii) since sub-centimetre lymphadenopathy in pSS detected by ultrasound or CT tends to remain stable overtime and probably does not represent a poor prognosis factor for pSS (16), we have included patients with lymph node enlargement of a diameter >1cm, to assess whether the presence of this easily assessed clinical feature could lead to the description of a distinct subgroup of pSS patients with specific clinical characteristics; iii) relatively large cohort of patients with pSS-related lymphadenopathy; iv) harmonised clinical data among the participating centres based on the HarmonicSS reference model to ensure high quality of data collection and processing, and v) analysis and comparison with both unmatched and matched control pSS patients without lymphadenopathy.

The prevalence of lymphadenopathy has been reported in approximately 10% of pSS patients (5). This is also

confirmed by the current study, since 13% of the pSS patients included developed lymphadenopathy, not related to lymphoma, during the disease course. In the unmatched comparison, patients with lymphadenopathy were characterised by a younger age at both pSS onset and diagnosis, as well as by shorter disease duration. In addition, patients with lymphadenopathy displayed more frequently SGE, higher FS at their first SG biopsy, extra-epithelial immune-complex mediated manifestations, such as palpable purpura, PNS involvement and glomerulonephritis, leukopenia, and autoantibodies. Similar findings were observed after comparing with matched for age, sex, and disease duration pSS controls without lymphadenopathy, although among serological parameters only anti-Ro/SSA retained their higher frequency for the lymphadenopathy group.

It has been previously shown that pSS patients with early disease onset display a distinct clinical phenotype and present more often lymphadenopathy (17). The present study is in accordance with this finding, showing that pSS patients with lymphadenopathy tend to be of younger age at pSS onset and diagnosis compared to pSS patients without lymphadenopathy. A previous study demonstrated that the extension of the SG inflammatory infiltration correlated with lymphadenopathy (18), while a more recent one reported that patients with a minor SG FS≥4 present more often with lymphadenopathy compared to those with FS<4 (19). The present study confirms the correlation of lymphadenopathy with higher FS at first SG biopsy. In the only published study describing the characteristics of pSS patients with lymphadenopathy, Elefante *et al*. reported that pSS patients with palpable lymphadenopathy express a more severe disease phenotype characterised by younger age at pSS diagnosis, more frequently male gender, higher disease activity, SGE, low C3 levels, hypergammaglobulinaemia, anti-Ro/SSA, anti-La/SSB and rheumatoid factor (RF) positivity, and cryoglobulinaemia (16). In the present study, we have accordingly demonstrated higher rates of SGE and anti-Ro/SSA positivity in the comparison between lymphadenopathy and matched non-lymphadenopathy patients, while higher rates of anti-La/SSB positivity were found only in the unmatched comparison. There were no differences between the lymphadenopathy and non-lymphadenopathy group regarding gender, RF positivity and cryoglobulinaemia.

Vasculitis and lymphoma are considered life-threatening complications of pSS (20) and patients with lymphadenopathy seem to display a clinical phenotype with vasculitic complications and a variety of lymphoma associated adverse prognostic factors. Extraepithelial vasculitic manifestations are observed in 10–15% of pSS defining a more systemic form of the disease (20, 21), and constitute major lymphoma predictors (22-24). In the lymphadenopathy group the vasculitic manifestations of palpable purpura, PNS involvement and glomerulonephritis were more frequent compared to the non-lymphadenopathy group, both in the unmatched and matched patient comparison. Interestingly, no differences were observed regarding RF positivity, C4 hypocomplementemia and cryoglobulinaemia. In addition, SGE is another strong prognostic factor for lymphoma (25), which was more prevalent in pSS patients with lymphadenopathy compared to their non-lymphadenopathy counterparts. Lymphopenia has been considered as a possible predictive factor for lymphoma development in some studies (26, 27), though not confirmed in more recent ones (4, 5). Leukopenia and neutropenia have also been identified as possible predictive factors for lymphomagenesis (26, 28, 29). In the lymphadenopathy group leukopenia and lymphopenia were shown to be more frequent compared to the matched non-lymphadenopathy group. Overall, it seems that pSS patients with lymphadenopathy accumulate features that are considered adverse prognostic factors for lymphoma development and should be carefully followed up by clinicians. In this line, previous studies have supported lymphadenopathy as predictive factor of lymphoma development (5, 23, 26, 30, 31), while activity in the lymphadenopathy domain of the ESSDAI at the time of pSS diagnosis has been associated with haematological cancer (32). Since the aim of the present study was to describe the clinical phenotype of pSS patients with lymphadenopathy, we have not addressed the question of lymphoma risk. A future prospective study of this subgroup of patients could provide information on the specific additional characteristics that may contribute to higher propensity for lymphomagenesis in the lymphadenopathy subset. Given that pSS lymphadenopathy reflects the expansion and antigenic stimulation of the B-cell component in disease pathogenesis, this subset of patients may be ideal to study the molecular mechanisms implicated in the crossword between autoimmunity and lymphomagenesis, as well as in the transition from the local to the systemic level of autoimmune response. In conclusion, pSS patients presenting with lymphadenopathy constitute a distinct clinical subgroup characterised by younger age at pSS diagnosis, shorter disease duration, more frequent SGE, higher FS at first SG biopsy, prominent autoantibody positivity and vasculitic extraepithelial manifestations, suggesting a strong and systemic B cell activation. Studies focusing on this subset of patients may provide further insights into the systemic nature of the disease and the related lymphomagenesis.

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