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To cite this article: L Vasaitis, G Nordmark, E Theander, C Backlin, KE Smedby, J Askling, L Rönnblom, C Sundström & E Baecklund (2018): Comparison of patients with and without pre-existing lymphoma at diagnosis of primary Sjögren’s syndrome, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2018.1523456

To link to this article: https://doi.org/10.1080/03009742.2018.1523456

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Comparison of patients with and without pre-existing lymphoma at diagnosis of primary Sjögren’s syndrome

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Objective: In the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren’s syndrome (pSS), pre-existing lymphoma is not an exclusion criterion for pSS diagnosis, as in earlier criteria. We aimed to explore whether there are differences between pSS patients with and without pre-existing lymphoma at pSS diagnosis.

Method: Patients with ICD–7–10 codes for Sjögren’s syndrome (SS) and a diagnosis of malignant lymphoma before or after SS diagnosis were identified by linking the Swedish Patient Register 1964–2007 with the Cancer Register 1990–2007 (n = 224). Clinical data were collected from medical records. Lymphoma diagnoses were evaluated by tissue review. Characteristics of pSS patients with and without pre-existing lymphoma were compared.

Results: We identified 107 patients with pSS as the reason for an SS diagnosis code and a verified lymphoma. Of these, 18 (17%) had a pre-existing lymphoma at pSS diagnosis, defined as lymphoma diagnosed before or within 6 months of pSS diagnosis. Male gender (39% vs 10%, p = 0.006), enlarged lymph nodes during the pSS disease (61% vs 27%, p = 0.01), mucosa-associated lymphoid tissue (MALT) lymphoma (50% vs 22%, p = 0.02), and salivary gland lymphoma (61% vs 26%, p = 0.006) were more common in patients with a pre-existing lymphoma at pSS diagnosis. Other pSS characteristics were similar.

Conclusion: In a substantial proportion of patients, particularly in men, pSS remains undiagnosed until after lymphoma diagnosis. The study highlights the importance of pSS investigation in patients with lymphoma, especially MALT lymphoma, in the salivary glands.

Primary Sjögren’s syndrome (pSS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration in exocrine glands, typically the lacrimal and salivary glands, causing the characteristic features of dry eyes and dry mouth.

Sicca symptoms are, however, not restricted to patients with pSS, but may develop for a wide spectrum of other reasons, including a malignant process such as lymphoma in the salivary or lacrimal glands. The shared sicca symptoms present in pSS and in a subset of lymphoma patients have led to a discussion of diagnostic difficulties, and it has been argued that patients with lymphoma cannot reliably be diagnosed with pSS. An increased risk of lymphoma is well described in pSS, and previous classification criteria for pSS have therefore incorporated pre-existing lymphoma as an exclusion criterion for a pSS diagnosis (1–3). Later, based on expert meeting consensus, this exclusion criterion was removed and it is not part of the American College of Rheumatology (ACR)/Sjögren’s International Collaborative Clinical Alliance (SICCA) 2012 classification criteria (4), or the 2016 ACR/European League Against Rheumatism (EULAR) classification criteria for pSS (5).

In this study, we wanted to explore the basis for pre-existing lymphoma as an exclusion criterion for a pSS diagnosis and to investigate whether there are differences in pSS patients with and without pre-existing lymphoma at pSS diagnosis. We took advantage of the Swedish national healthcare registries to identify a large population-based cohort of patients diagnosed with both Sjögren’s syndrome (SS) and lymphoma. The aim was to identify patients with pSS and compare both pSS and...
lymphoma characteristics in patients with or without pre-existing lymphoma at pSS diagnosis.

Method

Study population

A national population-based cohort of individuals with an inpatient or outpatient visit listing the diagnosis code for ‘Sjögren’s syndrome/sicca syndrome’ was identified using the Swedish National Patient Register (which includes inpatient care since 1964 and outpatient, non-primary care since 2001). All individuals with a diagnosis of SS as the main or secondary diagnosis in 1964–2007 were identified using the following International Classification of Diseases (ICD) codes (6): 374.06 (ICD-7), 734.90 (ICD-8), 710C (ICD-9), and M35.0 (ICD-10). For M35.0, the additional codes H19.3 (SS with keratoconjunctivitis), J199.0 (SS with pulmonary involvement), G73.7 (SS with myopathy), and N16.4 (SS with renal tubulointerstitial disease) were added. Through linkage with the Swedish Cancer Register, which covers > 95% of all incident cancer in Sweden (7), we identified all SS patients diagnosed with a lymphoid malignancy (ICD-7: 200–203) (hereafter called lymphoma) at ≥ 18 years of age in 1990–2007 (n = 224) irrespective of whether the haematological malignancy was diagnosed before or after the first registered SS diagnosis code in the Patient Register.

Evaluation of different conditions behind SS diagnoses and validation of pSS and lymphoma diagnoses

Detailed information about the SS diagnoses and the lymphomas was extracted from the patients’ medical records according to a comprehensive questionnaire. As the ICD codes for SS have not been used for pSS exclusively, but also for other causes of sicca symptoms, the underlying reason for the SS diagnosis code was carefully evaluated. Patients were grouped as pSS or non-pSS patients. Those with a clear explanation for the SS code other than pSS and/or no support for a pSS diagnosis in the medical records were considered as non-pSS patients. The patients grouped as pSS had been diagnosed with pSS by the treating physician and the available information in the medical records supported this diagnosis.

The archived lymphoma tissues of the patients in the pSS group were reviewed by a haematopathologist (CS) to confirm the lymphoma diagnosis and classify the lymphoma according to the World Health Organization classification (8). The patients in the pSS group with a confirmed lymphoma were evaluated for the fulfilment of the 2002 American–European Consensus Group (AECG) criteria for pSS (3) (lymphoma as an exclusion criterion was not employed) and the 2016 ACR/EULAR criteria for pSS (5). We excluded six patients from the study for administrative reasons (duplicates, error in coding, or medical records not found or too sparse), and 11 patients with no lymphoma upon tissue review.

Characteristics of pSS patients with and without pre-existing lymphoma

The patients in the pSS group were divided into those with and those without pre-existing lymphoma at pSS diagnosis. Date of pSS diagnosis was the diagnosis date documented in the medical records and date of lymphoma diagnosis was the date of first lymphoma diagnosis in the Cancer Register. We defined pre-existing lymphoma as lymphoma diagnosed before pSS diagnosis, or within 6 months after pSS diagnosis. This definition was chosen as signs of lymphoma were present at pSS diagnosis in these patients, although the final diagnoses were delayed. Clinical and laboratory data on the pSS disease were collected from the medical records from the onset of patient-reported sicca symptoms until 6 months before lymphoma diagnosis. All patients in the pSS group with confirmed lymphoma were followed up for overall survival from lymphoma diagnosis until 15 January 2017, at the latest.

Ethical approval was obtained from the Regional Ethical Review Board, Uppsala, Sweden.

Statistical analysis

Statistical analyses were performed using Statistica version 13 software (StatSoft, Tulsa, OK, USA). For continuous variables, the Mann–Whitney U-test was applied. For categorical variables, Fisher’s exact test was used to compare frequencies between groups. A value of p < 0.05 was considered statistically significant.

Results

Underlying reasons for an SS diagnosis code

After review of the medical records and lymphoma tissues, 207 patients with an SS diagnosis and a confirmed lymphoma were identified; 107 (52%) in the pSS group and 100 (48%) in the non-pSS group (Table 1). Of the 107 patients in the pSS group, 57 (53%) fulfilled the 2002 AECG criteria and 59 (55%) the 2016 ACR/EULAR criteria for pSS. The patients who did not fulfil these criteria typically had not been fully examined according to the criteria, or this information could not be found in the medical records. However, all available information, including presence of extraglandular manifestations and laboratory abnormalities, supported the pSS diagnosis. We could not detect that lymphoma was the underlying reason for the symptoms leading to
the SS diagnosis code in any of the patients in this study.

In the non-pSS patients, the most common cause of an SS diagnosis was secondary SS in association with another rheumatological disease (n = 54) (Table 1). The second largest group consisted of patients who had been fully investigated for sicca symptoms with an initial suspicion of pSS, but no support for this diagnosis after investigation (n = 15). Instead, these patients had other reasons, e.g. drug therapy, old age, or diabetes, as the final explanation for the sicca symptoms. Other more common reasons for an SS diagnosis code included isolated keratoconjunctivitis sicca (n = 12) and radiation therapy for cancer in the head–neck region (n = 11). One patient had previously been reported by us as having immunoglobulin G4 (IgG4)-related disease in an analysis of archived tissues (9) and was therefore included in this study with the correct diagnosis, namely IgG4-related disease with sicca symptoms, in the non-pSS group (Table 1).

Comparison of pSS patients with and without pre-existing lymphoma

In this analysis, we included 105 patients from the pSS group. Two patients with pSS according to both the 2002 and 2016 classification criteria and diffuse large B-cell lymphoma were not included as the lymphomas occurred shortly (2 and 9 months) after organ transplantation, which is associated with an increased risk for the development of lymphoma. Of the 105 patients, a total of 18 individuals (17%) had a pre-existing lymphoma at pSS diagnosis (four patients with lymphoma diagnosed 1–5 years before pSS diagnosis, and 14 diagnosed with lymphoma within 6 months after pSS diagnosis).

Comparison of the features of the 18 pSS patients with pre-existing lymphoma with the 87 pSS patients with lymphoma after pSS diagnosis showed that male gender and enlarged lymph nodes during the pSS disease were more common among patients with pre-existing lymphoma at pSS diagnosis (Table 2). There were no significant differences in other demographic, clinical, and laboratory pSS findings. Thus, the median ages at sicca onset and pSS diagnosis, the median time from patient-reported sicca onset until pSS diagnosis, and the presence of extraglandular pSS manifestations and auto-antibodies were similar in both groups.

Some differences were noted between the two groups regarding the lymphoma characteristics (Table 2). Patients with pre-existing lymphoma at pSS diagnosis more often had an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type (50% vs 22%, p = 0.02) and lymphoma localized in the major salivary glands (61% vs 26%, p = 0.006) compared with patients in the group with a lymphoma diagnosed after pSS diagnosis.

Table 1. Underlying conditions in 207 patients with an International Classification of Diseases code of ‘Sjögren’s syndrome/sicca syndrome’ and a lymphoma identified through linkage between the Swedish Patient Register (1964–2007) and the Cancer Register (1990–2007), and the lymphoma verified by tissue review.

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>Number of patients n = 207 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSS diagnosis*</td>
<td>107 (52)</td>
</tr>
<tr>
<td>Fulfilling the 2002 AECG criteria for pSS (3)</td>
<td>57 (28)</td>
</tr>
<tr>
<td>Fulfilling the 2016 ACR/EULAR criteria for pSS (5)</td>
<td>59 (28.5)</td>
</tr>
<tr>
<td>Non-pSS diagnosis</td>
<td></td>
</tr>
<tr>
<td>Secondary SS or overlap syndrome:</td>
<td>100 (48)</td>
</tr>
<tr>
<td>Rheumatoid arthritis and SS</td>
<td>54 (26)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus and SS†</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Systemic sclerosis and SS‡</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Other causes of SS diagnosis</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Sicca symptoms, various reasons§</td>
<td>46 (22)</td>
</tr>
<tr>
<td>Keratoconjunctivitis sicca only</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy head–neck before sicca onset</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Graft-versus-host disease with sicca symptoms</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Sarcoidosis with sicca symptoms</td>
<td>5 (2)</td>
</tr>
<tr>
<td>IgG4-related disease with sicca symptoms¶</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

* Including two patients with primary Sjögren’s syndrome (pSS) with possible transplantation-associated lymphoma.
† Including one patient with overlap systemic lupus erythematosus and pSS (fulfilling criteria for both diseases).
‡ Including one patient with overlap systemic sclerosis and pSS (fulfilling criteria for both diseases).
§ Investigation according to the AECG criteria (3) excluded pSS; reasons include drugs, old age, and diabetes.
|| Investigation according to the AECG criteria (3) excluded pSS.
¶ Described in Vasaitis et al (9).
AECG, American–European Consensus Group; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; SS, Sjögren’s syndrome; IgG4, immunoglobulin G4.

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When we performed the same analysis restricted to the 55 patients fulfilling the 2002 AECG criteria for pSS (excluding the two with possible transplantation-related lymphomas), the results were comparable (Table 2). Of the 55 patients, nine (16%) had a pre-existing lymphoma at pSS diagnosis (three patients with lymphoma diagnosed 1–5 years before pSS diagnosis, and six diagnosed with lymphoma within 6 months after pSS diagnosis).

### Discussion

In this population-based study of patients with a diagnosis of both SS and lymphoma, we found that most pSS characteristics were similar irrespective of whether the patients had a pre-existing lymphoma at pSS diagnosis or whether pSS was diagnosed long before the lymphoma. These results support the decision to remove pre-existing lymphoma as a general exclusion criterion for pSS classification, as has been done in the ACR/SICCA 2012 criteria (4) and in the 2016 ACR/EULAR criteria for pSS (5). A relatively large proportion of patients with pSS (17% in this study) would not have been correctly classified with pSS if lymphoma had been employed as an exclusion criterion.

We observed that the patients with pre-existing lymphoma before pSS diagnosis in general did not seek medical care for the long-standing sicca symptoms due to pSS, but instead came to medical attention because of lymphoma symptoms, in most cases a swollen salivary gland or lymph node caused by a lymphoma. There was a higher frequency of men with pre-existing lymphoma compared with pSS patients with lymphoma after pSS diagnosis. One may speculate that men may be less prone to seek medical attention for sicca symptoms and will only be diagnosed with an underlying pSS once a

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**Table 2. Comparison of characteristics in 105 patients with primary Sjögren’s syndrome (pSS) according to the treating physician and 55 patients with pSS according to the 2002 American–European Consensus Group (AECG) criteria for pSS and a verified lymphoma, divided into those with and without pre-existing lymphoma at pSS diagnosis.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>According to treating physician (n=105)</th>
<th>According to AECG 2002 criteria (n=55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td>Present n=18</td>
<td>Not present n=87</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (61)</td>
<td>78 (90)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age at reported sicca onset (years)</td>
<td>61 (28–72)</td>
<td>48 (14–78)</td>
<td>0.2</td>
</tr>
<tr>
<td>Age at pSS diagnosis (years)</td>
<td>61 (43–79)</td>
<td>55 (14–78)</td>
<td>0.7</td>
</tr>
<tr>
<td>Time from sicca onset to lymphoma diagnosis (years)</td>
<td>6 (0–21)</td>
<td>13 (0–54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall survival from lymphoma diagnosis (years)</td>
<td>10 (0–18)</td>
<td>9 (0–24)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Clinical pSS characteristics†</strong></td>
<td>Present n=18</td>
<td>Not present n=87</td>
<td></td>
</tr>
<tr>
<td>Salivary gland swelling</td>
<td>11/18 (61)</td>
<td>45/84 (54)</td>
<td>0.6</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>11/18 (61)</td>
<td>41/84 (49)</td>
<td>0.1</td>
</tr>
<tr>
<td>Anti-SSA and/or anti-SSB</td>
<td>9/11 (82)</td>
<td>43/63 (68)</td>
<td>0.7</td>
</tr>
<tr>
<td>Rheumatoid factor positivity</td>
<td>7/19 (78)</td>
<td>42/66 (66)</td>
<td>0.7</td>
</tr>
<tr>
<td>Leucopenia (leucocytes &lt; 4.0 × 10⁹)</td>
<td>0/16 (0)</td>
<td>11/66 (17)</td>
<td>0.1</td>
</tr>
<tr>
<td>Thrombocytopenia (platelets &lt; 150 × 10⁹)</td>
<td>1/16 (6)</td>
<td>5/66 (8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypergammaglobulinaemia (IgG &gt; 15 g/L)</td>
<td>8/11 (73)</td>
<td>28/61 (48)</td>
<td>0.2</td>
</tr>
<tr>
<td>Clonal component in serum</td>
<td>1/10 (10)</td>
<td>9/60 (15)</td>
<td>0.1</td>
</tr>
<tr>
<td>Any immune-modulating treatment for pSS§</td>
<td>5/18 (28)</td>
<td>23/85 (39)</td>
<td>1</td>
</tr>
<tr>
<td>Salivary gland involvement of lymphoma</td>
<td>11/18 (61)</td>
<td>23/87 (26)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are shown as n (%), median (range), or n/available (%).

* Defined as lymphoma diagnosed before pSS diagnosis or within 6 months after pSS diagnosis.
† Ever during the period from reported onset of sicca symptoms until 6 months before lymphoma diagnosis.
‡ Palpable purpura/skin vasculitis, peripheral neuropathy, interstitial lung disease, myositis, arthritis, Raynaud’s, and/or nephritis.
§ Corticosteroids, antimalarials, azathioprine, methotrexate, and/or cyclophosphamide for ≥ 4 weeks.
ANA, antinuclear antibodies; SSA/SSB, Sjögren’s syndrome A and B antibodies; IgG, immunoglobulin G; MALT, mucosa-associated lymphoid tissue.
lymphoma is present. In a general population, there is a slight female preponderance of MALT lymphoma (8). The finding of a male predominance of MALT lymphoma among the patients with pre-existing lymphoma in this study may indicate gender differences regarding lymphoma risk in pSS patients. This notion also has support from a study of almost 1000 patients with pSS, in which lymphoma was more common among the men compared to the women with pSS (10).

A missed diagnosis of pSS is disadvantageous for the patient, as the disease will not be properly treated and extraglandular pSS manifestations may be misinterpreted as being lymphoma related. Highly active pSS is per se a prognostic factor for progression of lymphoma in pSS (11). There is also some support for lymphoma in pSS patients needing another lymphoma treatment compared to lymphoma in non-pSS patients. Several reports indicate that rituximab, a treatment option for MALT lymphoma, is less efficient in pSS patients with MALT lymphoma in the salivary glands compared with other sites or lymphoma subtypes (12–14).

In this population-based study of patients with a diagnosis of both SS and lymphoma, we found that not more than approximately half of the patients had pSS as the underlying cause of the SS diagnosis code, around 25% had secondary SS and 25% various other reasons for the SS diagnosis. The sicca symptoms were not directly attributed to lymphoma by the treating physician in any of the patients. This is the first study reporting the use of the SS diagnosis code in clinical practice. The many different underlying causes of sicca symptoms assigned to the same ICD code have several implications for the interpretation of register-based information and pose particular problems for studies of pSS. Thus, register-based information regarding SS diagnoses must be interpreted with caution and should be properly validated. In the current study, we noted that the SS code had not been used to diagnose and register sicca symptoms caused by lymphoma. Whether this reflects that sicca symptoms, in fact, are rare as a consequence of lymphoma, or whether haematologists and oncologists generally do not register this symptom separately, needs to be studied further.

Strengths of the present investigation include the population-based setting using high-quality registers in long-term use, and the careful validation of diagnoses from medical records and lymphoma tissue review. Some limitations should be acknowledged. The retrospective design may result in missed historical data. Furthermore, the different classification criteria for pSS during the study period resulted in incomplete investigations for the 2002 AECG and the 2016 ACR/EULAR pSS criteria in a subset of the patients owing to missing items in the medical records.

In the pSS group, we included both patients who formally did not fully satisfy the classification criteria owing to missing data. The patients who did not fulfil the criteria were carefully evaluated and all available information, including extraglandular manifestations and laboratory abnormalities, supported the pSS diagnosis and no other diagnosis. We also performed a comparison of the patients who fulfilled formal pSS classification criteria and those who did not, and found that most clinical and laboratory pSS characteristics were similar on the group level (Supplementary table S1), supporting that the pSS group was homogeneous and the patients were comparable. Sicca onset was recorded at the time of subjective dryness symptoms as noted in the medical records, and recall bias cannot be excluded. We also cannot exclude that oncologists may have underreported or not registered sicca symptoms in patients with lymphoma.

Conclusion

In this study, patients with pSS and pre-existing lymphoma were more often men and more often had lymphadenopathy compared with pSS patients who were diagnosed with lymphoma after the pSS diagnosis. However, there were no differences in other pSS characteristics, such as laboratory parameters or the presence of autoantibodies. It may be concluded that patients with lymphoma, in particular MALT lymphoma, in the major salivary glands should be investigated for pSS.

Acknowledgements

We would like to express our gratitude to Fredrik Granath (Karolinska Institutet, Stockholm, Sweden) for his help with register data. This study was supported by ALF funding from the County Council of Uppsala, Sweden, the Swedish Cancer Society, the Lions Cancer Research Foundation, Uppsala, Sweden, the Swedish Rheumatism Association, the Swedish Society of Medicine, King Gustav V’s 80 year foundation, and scholarships from Agnes & Mac Rubberg’s and Gustav Prim’s foundations.

Disclosure statement

No potential conflict of interest was reported by the authors.

References


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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary table S1 Comparison of characteristics of patients with primary Sjögren’s syndrome (pSS) according to the 2002 American–European Consensus Group (AECG) criteria.

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