Predictors for the development of non-Hodgkin lymphoma in primary Sjögren’s syndrome

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Summary
Sjögren’s syndrome (SS) is a complex autoimmune disease with multi-organ involvement. Its most serious complication is the development of non-Hodgkin lymphoma (NHL). In cohorts of unselected patients with long observation, this lifetime risk is estimated to be 5 to 15%, or approximately 20 times increased risk compared to the general population. Being able to identify patients prone to malignancy would significantly aid in the process of customised treatment and strategy for follow-up. Among the established predictors for lymphoma development in SS, we recognize recurrent or permanent swelling of major salivary glands (SG), lymphadenopathy, cryoglobulinemia, splenomegaly, low complement levels of C4 and C3, lymphopenia, skin vasculitis or palpable purpura, M-component in serum or urine, peripheral neuropathy, glomerulonephritis and elevated beta2-microglobulin. More recent suggestions include some genetic factors, CD4 lymphocytopenia, and ectopic germinal center-like structures in minor SG biopsies. Despite these predictors, there remains a need for defining algorithms for NHL screening and patient follow-up in SS.

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such as autoantibodies to Ro/SSA and/or La/SSB or positive rheumatoid factor and antinuclear antibodies titre ≥ 1:320, or a minor SG biopsy with focal mononuclear cell inflammation needs to be ascertained [2,3], as illustrated in Figure 1.

In addition to dryness symptoms, at least 1/3 of the patients also suffer from extra glandular manifestations of internal organs, and up to 50% of patients have fatigue and reduced health related quality of life. The main threat to patients with pSS is the increased risk of developing non-Hodgkin lymphoma (NHL). Thus far, development of NHL has primarily been studied in pSS [6–9].

**Sjögren’s syndrome and the risk of lymphoma development**

The connection between SS and NHL has been studied over the last 40 to 50 years. At first, the risk was overestimated due to the fact that patient included in the cohorts had been selected [10]. Presently, in unselected patient cohorts with long observation times and registry collaborations, the lifetime risk is estimated to 5 to 15%, or approximately 20 times increased risk compared to the general population [11]. Table 1 [10–16] provides an overview of important prevalence studies. The risk for NHL associated with pSS is higher than for SLE (7 times increased risk), RA (3 times increased risk) or other systemic AID [11].

**Subtypes of lymphomas**

Several subtypes of NHL have been described associated with pSS. Diffuse large B-cell lymphoma (DLBC) and mucosa-associated lymphoid tissue (MALT) lymphoma make up the most common types. MALT lymphoma in the SG is virtually always associated with pSS [17]. Smedby et al. showed a 28 times increased risk of MALT lymphoma and 11 times increased risk of DLBC associated with pSS [18]. At the International Symposium for SS in Athens, Greece 2011, Vasaitis et al. presented a similar risk for MALT or DLBC when more than 50 pSS-associated lymphomas were analyzed [19].

The type of NHL significantly determines both treatment and survival. In this respect, Pollard et al. have constructed an algorithm for treatment of pSS-associated MALT lymphoma, depending on the pSS disease activity, and the types of symptoms such lymphoma carries [20]. Previous studies indicate a short survival for aggressive DLBC; in our material 31 months for DLBC compared to 76 months for MALT [15]. Survival data for pSS-associated NHL following treatment with more recent treatment methods including combinations of

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**Table 1**

Studies on primary Sjögren’s syndrome and the risk of non-Hodgkin lymphoma (NHL)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>SIR (95% CI)</th>
<th>Number of patients</th>
<th>Number of NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kassan [10]</td>
<td>1978</td>
<td>USA</td>
<td>44.4 (16.7–118.4)</td>
<td>142</td>
<td>7</td>
</tr>
<tr>
<td>Kauppi [12]</td>
<td>1997</td>
<td>Finland</td>
<td>8.7 (4.3–15.5)</td>
<td>676</td>
<td>11</td>
</tr>
<tr>
<td>Pertovaara [13]</td>
<td>2001</td>
<td>Finland</td>
<td>13 (2.7–38.0)</td>
<td>110</td>
<td>3</td>
</tr>
<tr>
<td>Lazarus [14]</td>
<td>2006</td>
<td>UK</td>
<td>37.5 (20.7–67.6)</td>
<td>112</td>
<td>11</td>
</tr>
<tr>
<td>Theander [15]</td>
<td>2006</td>
<td>Sweden</td>
<td>15.6 (7.8–27.9)</td>
<td>286</td>
<td>12</td>
</tr>
<tr>
<td>Zhang [16]</td>
<td>2010</td>
<td>China</td>
<td>48.1 (20.7–94.8)</td>
<td>1320</td>
<td>8</td>
</tr>
</tbody>
</table>

SIR: standardized incidence ratio; CI: confidence interval.
chemotherapeutic drugs and rituximab (anti-CD20 treatment) are not available yet.

**Prediction of primary Sjögren’s syndrome-associated non-Hodgkin lymphoma**

In the majority of cases, patients with pSS are followed in the primary care system, in close collaboration with a rheumatologist, a general dentist, and an ophthalmologist. How can one determine which patient belong to the 10 to 15% who eventually will develop a NHL complicating their pSS? Being able to recognize these patients would significantly aid in the process of customised treatment and strategy for their follow-up (table II).

Certain predictors have long been well known [21–24], and subsequently confirmed in several studies, whereas others are more recent suggestions [15,25–27].

We have recently shown [25] an increased risk of NHL in patients with so-called germinal center (GC)-like structures in the diagnostic minor SG lip biopsy (GC+ patients) compared to patients lacking such organisation (GC- patients [25], as shown in figures 2 and 3).

A genetic polymorphism has been associated with the development of AID, as well as with that of NHL. These AID include pSS [26]. Worthwhile to note is that in the cohort of lymphoma patients (n = 12), 7 harbor some kind of mutation in the so-called A20 gene.

Individuals with several risk factors or several overlapping AID have most likely an increased risk of pSS-associated NHL [16,23]. Male patients with pSS seem to have a somewhat higher risk of NHL compared to female patients [28] and with longer disease duration, the risk of NHL increases [15,19,29]. For RA, the risk of NHL is clearly linked to high disease activity [30]. Measures for disease activity, termed EULAR SS Disease Activity Index (ESSDAI), are fairly new in pSS [31]. Many of the aforementioned risk factors are part of this multivariable tool, and one can assume that high ESSDAI scores over time will be associated with development of NHL in pSS.

**Different risk factors for different types of lymphoma?**

Preliminary findings suggest the occurrence of MALT lymphoma primarily in younger patients, earlier in their pSS disease course, and more frequently in patients with hypergammaglobulinaemia. DLBc seems to occur at a later stage and in patients with cytopenias in their disease history [19,23]. It is also possible that some of the DLBc lymphomas develop as a progression of MALT to DLBC. The prevalence of this development in pSS remained to be determined.

**Pathogenesis of lymphoma development**

Predisposing factors for development of lymphoproliferative diseases in patients with AID are not clearly defined. Autoimmunity and malignancy both express a misconduct in immunity and tolerance. A cooperation between genetic predisposition and external factors such as infections, toxins and
trauma, certainly represents such conditions. This hypothesis is supported by the more recent predictors CD4+ T-lymphytopenia (typical factor in an HIV infection), formation of GC-like structures (B-cell maturation with multiple replication steps where mutations may occur), and mutations in the A20 gene [26], a gene associated with both autoimmunity and lymphoma (table II).

In about 25% of patients with pSS, the glandular lymphoid infiltrates are organized into structures resembling GC of secondary lymphoid tissue [25,32–39]. Morphologically, these GC-like structures in the minor SG are characterized by a well-circumscribed chronic inflammatory cell infiltrate consisting of at least 50 mononuclear cells, and presenting with features indicative of lymphoid organisation such as a densely packed dark zone and a light zone, within otherwise normal SG epithelium (figure 3). Lymphoid organisation is not observed in conventional focal infiltrates (figure 1). Of note, focal infiltrates and GC-like structures may coexist within the same minor SG [34]. In normal GC, B-cells enter the outer dark zone of these structures after antigen-stimulation and T-cell co-activation, in order to undergo somatic hyper mutation. Subsequently, the cells enter the light zone, where the affinity of the rearranged immunoglobulin gene products is tested on the antigen presented by the follicular dendritic cells (FDC). Ectopic GC-like structures in the minor SG present with FDC networks, organization/T and B-cell compartments, and proliferation. FDC networks can be characterized by immunohistochemistry, by staining with monoclonal antibodies against CD21, CD23 or CD35 [34]. B and T cells compartments are detected by CD20 and CD3/CD4, and proliferating cells by Ki-67 [38,40]. In normal GC, the cells that survive apoptosis are stimulated by T cells to undergo class switch recombination and further differentiation.

**Figure 2**

Development of non-Hodgkin lymphoma in patients with primary Sjögren’s syndrome with or without germinal center-like structures in their minor salivary gland lip biopsy [25]

**Figure 3**

Minor salivary gland biopsy with a germinal center-like structure
into antibody-producing plasma cells or memory B cells [38,39]. B cells in ectopic GC also undergo somatic hyper mutation and antigen-driven selection of the variable region genes of immunoglobulins. In pSS, the patterns of aberrant mutations suggest that the glanular microenvironment supports the GC reaction in a different manner than secondary lymphoid tissue [41]. Polyclonal B-cell infiltration may, under certain circumstances continue into a polyclonal B-cell proliferation which in turn may mature to monoclonal, originally benign to malignant [40,41]. There are several potential consequences of such ectopic GC-like structures affecting disease expression. Firstly, they might have a detrimental effect on the glandular architecture causing increased functional disability [35]. Secondly, GC-formation could increase the effectiveness of the communication between lymphocytes and thus a more efficient immune apparatus with potential for aggravating the disease course could follow, e.g., through immune complex formation [39]. Thirdly, these formations could also precede the development of NHL since this process seems to rely on an antigen-driven stimulation [40,41].

**Suggested strategies for patient follow-up**

Currently, there are no publicly available algorithms for NHL screening and follow-up of patients with pSS. We recommend a thorough examination of the individual patient, preferentially with regard to ESSDAI variables. Using ESSDAI, most important risk factors are evaluated. In addition, a thorough anamnesis/medical history to define duration of disease, as longer disease duration predisposes to a higher risk of malignancy, in particular the aggressive but treatable DLBC. In addition, a combination of several AID most likely increases the risk of NHL. Important diseases to consider are thyroid disease, coeliac disease, psoriasis, and inflammatory bowel disease. Furthermore, evaluation of the minor SG lip biopsy, with focus score and determination of GC-like structures should be considered [25]. Patients with two or more risk factors should be closely followed and require a more targeted disease evaluation, if suspicion of lymphoma arises.

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