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Clinical features distinguishing lymphoma development in primary Sjögren's syndrome—A retrospective cohort study ☆

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ABSTRACT

Objective: The objective is to determine the relationship between clinical features and non-Hodgkin lymphoma (NHL) development in primary Sjögren's Syndrome (pSS), taking recently designed disease activity/severity scores into account.
Methods: Medical charts of pSS patients were retrospectively analyzed, scoring first and last visits with the (cumulative) EULAR Sjögren's Syndrome Disease Activity Index and counting extraglandular manifestations, comparing patients with and without NHL.
Results: One hundred ninety-five patients were analyzed with a median follow-up of 92 months (range 12–256). Twenty-one patients (11%) had NHL. Associations of parotid gland enlargement (OR 2.84) and low C4 (OR 7.71) with NHL were confirmed. In NHL patients, development of purpura, peripheral neuropathy (PNP), and glomerulonephritis (GN) concurred with lymphoma in 3/3, 5/7, and 2/2 of cases, respectively. Otherwise, purpura and PNP were not associated with NHL later on. This suggests that these symptoms might represent paraneoplastic events (in 16%, 24%, and 100% of our cases, respectively). Presence of IgM-kappa clonal components was associated with lymphoma in 64% of cases. Disease activity/severity scores at first visit could not predict lymphoma development, nor was the pSS disease course significantly worse in patients with NHL.
Conclusions: In our cohort, no clinical manifestation or disease score could clearly select patients with subsequent lymphoma development. Presence of IgM-kappa clonal components and development of purpura, PNP, and GN should alert the clinician for the presence of lymphoma.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by B-cell hyperactivity and lymphocyte infiltration of exocrine glands, predominantly salivary and lacrimal glands. Clinically, this leads to symptoms of xerostomia and xerophthalmia, and the presence of autoantibodies and hypergammaglobulinemia in blood. Additionally, extraglandular disease manifestations can occur. However, pSS disease expression is relatively stable over time in most patients [1].

The incidence of B-cell non-Hodgkin lymphoma (NHL) is elevated in patients with pSS. Several reports indicate a 16–18-fold increase compared to the general population [2–4]. Marginal zone lymphoma (MZL), either nodal or extranodal (of the mucosa-associated lymphoid tissue/MALT type), and diffuse large B-cell lymphoma (DLBCL) are most commonly seen. Occurrence of lymphoma is associated with an increased mortality rate [5,6].

Lymphoma development is thought to be the result of a multistep process involving B–T cell interactions in the glandular infiltrates. Effective antigen presentation and B-cell facilitation leads to local production of autoantibodies directed against Ro/Sjögren's Syndrome A (SSA), La/Sjögren's Syndrome B (SSB), and gammaglobulin (rheumatoid factor, RF) [7,8]. Ongoing antigen stimulation can promote clonal expansion of B cells with the presence of clonal components in blood, which is a hallmark of pSS [9]. The same clone can be seen at several locations persisting in time, or different clones can dominate per location and time interval [10,11]. Eventually, malignant transformation may occur. Progression of low-grade into high-grade tumors has been shown [1], as well as hematogenous dissemination of malignant clones from salivary glands to lymph nodes [12].

The increased incidence of lymphoma has stimulated research, especially focusing on predictive parameters present at the time of pSS diagnosis. Commonly implicated as risk factors are parotid gland enlargement, purpura, peripheral neuropathy (PNP), hypocomplementemia, and cryoglobulinemia [1,2,4,5,13]. In these studies, the time intervals between the occurrence of these signs and lymphoma were not reported.

Lymphoma can induce paraneoplastic manifestations, like neuropathy and vasculitis [14–17]. The same symptoms may also

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occur as extraglandular manifestations of pSS. Differentiating between these 2 causes can be difficult. The indolent nature of most pSS-related lymphoma obscures their detection. Since sicca symptoms have usually been present 7 years prior to the diagnosis of pSS [1,2], a complicating NHL could already have developed.

Our objective was to reassess the relation between clinical features and NHL development in pSS patients, taking recently designed disease activity/severity scores into account.

Patients and methods

Study cohort

Medical charts of all patients with a diagnosis of Sjögren's Syndrome (based on ICD-9/10 coding) from the period 1998 until July 2011 were retrospectively analyzed. Only patients with primary Sjögren's syndrome based on the 2002 classification criteria were included [18], excluding patients with concomitant diagnosis of other connective tissue diseases. Patients had to have visited our out-patient clinic regularly, with at least 2 visits more than 1 year apart. Only the first and the last visit were scored using disease activity/severity scores; the time in between is the follow-up time. Digital patient data were available from January 1, 1990 onwards, being the first possible date for a first study-cohort visit. The retrospective and anonymous nature of this report makes ethical approval unnecessary, following the ethics guidelines of our hospital.

Scoring of disease manifestations

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) was used to score disease activity at the first visit. The ESSDAI consists of 12 domains with an assigned weight factor (n), namely constitutional (3), lymphadenopathy (4), glandular (2), articular (2), cutaneous (3), pulmonary (5), renal (5), muscular (6), peripheral nervous system (5), central nervous system (5), hematological (2), and biological (1). For each domain, the severity of the manifestation is scored as absent (=0), low (=1), moderate (=2), or high (=3). These counts are then multiplied by the assigned weight factor. Total scores can range between 0 and 123 points [19]. For calculating ESSDAI scores, missing laboratory data were interpreted as being normal or absent if no value was available for any time point, the last value was carried forward, or the first value was carried backward.

Additionally, the number of clinical extraglandular manifestations (EGM) present at the first visit was counted, using the same definitions as ESSDAI but without a severity index or weight factor. The EGM scored were white blood cell abnormality (neutropenia, lymphopenia, or leukopenia), anemia, vasculitis/purpura, other skin manifestations [subacute cutaneous lupus erythematosus (SCLE), erythema marginatum], arthritis or arthralgia, interstitial lung disease (ILD), renal manifestations (tubular acidosis, tubular interstitial disease, or glomerulonephritis), central nervous system manifestations, peripheral neuropathy (PNP), myositis, lymphadenopathy, and non-Hodgkin lymphoma. To gain insight into the severity of the pSS disease course a "total cumulative ESSDAI score" was calculated, summating the maximum scores per organ domain achieved at any time point in life [20]. Similarly, "total EGM" were counted. Parotid gland enlargement had to have been observed clinically to be counted as glandular manifestation.

For analysis of correlations between disease activity scores at first visit and lymphoma development, patients with (history of) lymphoma present at the first visit were excluded (No 1, 4, 5, and 9). Non-Hodgkin lymphoma were categorized according to the WHO classification and staged according to the Ann Arbor system.

Ranges of laboratory parameters

Laboratory data were interpreted according to our hospital references [University Medical Centre Utrecht (UMCU), the Netherlands], or according to the ESSDAI definitions when stated and applicable. Anemia was defined as a hemoglobulin level <12 g/dL/ <7.5 mmol/L (ESSDAI/UMCU), leukopenia as $<4.0 \times 10^9$/L (UMCU), lymphopenia as $<0.8 \times 10^9$/L (UMCU), neutropenia as $<1.6 \times 10^9$/L (UMCU), thrombocytopenia as $<150 \times 10^9$/L (ESSDAI/UMCU), low complement 3 (C3) and 4 (C4) as <0.90 g/L (UMCU) and <0.10 g/L (UMCU), respectively, hypergammaglobulinemia as ≥ 16.0 g/L (ESSDAI/UMCU), and hypogammaglobulinemia as <7.0 g/L (UMCU).

Statistical analysis

Analyses were carried out using SPSS 15.0. Mann–Whitney U test was used to compare unpaired, non-categorical data. Chi-square test for independence was used to explore the relationship between categorical variables, significance was determined by Fisher's exact Test. Additionally, Odd Ratios (OR) were calculated. A 2-sided p value <0.05 was considered significant.

Results

Demographics

In total, 195 patients with a median follow-up of 92 months (range 12–256) were included. Non-Hodgkin lymphoma was seen in 21 patients (11%). Table 1 displays NHL group characteristics, and Table 2 shows features of individual NHL patients. Several patient characteristics were compared between patients with and without NHL diagnosis (Table 3).

(Extra-) glandular manifestations distinguishing NHL development

Peripheral neuropathy was significantly more common in patients with NHL ($p = 0.0003$): 7/21 (33%) patients versus 14/174 (8%) patients without symptoms of NHL during follow-up of median 72 months (range 15–252). Sensory axonal polyneuropathy and sensorimotor neuropathy were significantly more common in NHL patients ($p = 0.018$ and $p = 0.031$, respectively). Mononeuritis multiplex was seen in 2 patients without lymphoma (1%; follow-up of 28 and 50 months), and in 1 lymphoma patient, sensorimotor neuropathy evolved into mononeuritis multiplex during lymphoma progression ($p = 0.29$). Facial nerve palsy was seen in 1 lymphoma patient with progressive disease, who also had sensory axonal neuropathy. When looking into time

Table 1
Demographics of patients with non-Hodgkin lymphoma

Characteristic	$n = 21$
Age at NHL diagnosis (y), median (range)	59 (36–69)
Time between pSS and NHL diagnoses (m), median (range)	82 (−6 to 264)
MALT lymphoma	10 (48)
Nodal marginal zone lymphoma	3 (14)
Diffuse large B-cell lymphoma	8 (38)
Lymphoma-related death	3 (14)

Values are displayed as number (percentage), unless otherwise specified. NHL, non-Hodgkin lymphoma; y, years; m, months; MALT, mucosa-associated lymphoid tissue.