EXTENDED REPORT

A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study

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Objective: To investigate risk factors for non-Hodgkin's lymphoma (NHL) and analyse NHL subtypes and characteristics in patients with systemic lupus erythematosus (SLE).

Methods: A national SLE cohort identified through SLE discharge diagnoses in the Swedish hospital discharge register during 1964 to 1995 (n = 6438) was linked to the national cancer register. A nested case control study on SLE patients who developed NHL during this observation period was performed with SLE patients without malignancy as controls. Medical records from cases and controls were reviewed. Tissue specimens on which the lymphoma diagnosis was based were retrieved and reclassified according to the WHO classification. NHLs of the subtype diffuse large B cell lymphoma (DLBCL) were subject to additional immunohistochemical staining using antibodies against bcl-6, CD10 and IRF-4 for further subclassification into germinal centre (GC) or non-GC subtypes.

Results: 16 patients with SLE had NHL, and the DLBCL subtype dominated (10 cases). The 5-year overall survival and mean age at NHL diagnosis were comparable with NHL in the general population—50% and 61 years, respectively. Cyclophosphamide or azathioprine use did not elevate lymphoma risk, but the risk was elevated if haematological or sicca symptoms, or pulmonary involvement was present in the SLE disease. Two patients had DLBCL-GC subtype and an excellent prognosis.

Conclusions: NHL in this national SLE cohort was predominated by the aggressive DLBCL subtype. The prognosis of NHL was comparable with that of the general lymphoma population. There were no indications of treatment-induced lymphomas. Molecular subtyping could be a helpful tool to predict prognosis also in SLE patients with DLBCL.

Evidence of an increased risk to develop haematological malignancy, and especially non-Hodgkin's lymphoma (NHL) in autoimmune diseases, has been gathered since the 1970s. First studies of Sjögren's syndrome,[1] then rheumatoid arthritis (RA)[2] and now in the last decade studies from uni-/multicentre SLE cohorts[3–8] and national SLE cohorts[9 10] have consistently shown a markedly increased risk of NHLs. As for NHL subtype, knowledge is more limited. RA and SLE share several disease manifestations like arthritis and ''extra-articular manifestations'' such as serositis, sicca symptoms and interstitial inflammatory lung disease. In RA, a pronounced overrepresentation of diffuse large B cell lymphoma (DLBCL) has been reported from a large population-based cohort.[11] This lymphoma subtype was also the most frequent in an international multicentre study with lupus patients.[12] In Sjögren's syndrome, approximately 85% are MALT lymphomas,[13] although a recent study from a mono-centre primary Sjögren's syndrome cohort—with patients fulfilling the American–European Consensus Group criteria[14]—showed a predominance of DLBCL.[15]

The pathophysiological mechanisms for the enhanced risk of developing NHL in patients with chronic inflammatory diseases are still not fully understood. Similarities of a variety of immunological disturbances that characterise both rheumatic conditions and lymphomas have been suggested as a linkage between these disorders as well as a possible potentiation of immunosuppressive drugs or certain viral infections, especially Epstein–Barr virus (EBV).[5 16]

Recently, advances in molecular characterisation have enabled more detailed subclassification of lymphomas based on the molecular expression of the tumour cells. For DLBCL, two prognostic groups have been identified among DLBCL in the general lymphoma population depending on the resemblance of gene expression profile with normal germinal centre (GC) or activated B cells by using global gene expression profiling[17 18] and immunophenotyping of tumour cells.[19 20] The GC DLBC lymphomas had a significantly better survival than those with non-GC subtype.[17–20] No such subtyping has been reported in SLE patients.

In a previous register study of a population-based national Swedish SLE cohort, a threefold increased risk of lymphoma was found.[10] This nested case-control study focuses on those SLE patients that developed NHL. Information on clinical manifestations and pharmacological (cytotoxic) treatment of the SLE disease was retrieved from patient records. The lymphomas were re-examined and reclassified, and DLBCLs were further divided into GC or non-GC subtypes by immunohistochemistry. The presence of EBV in the lymphomas was also analysed.

PATIENTS AND METHODS

Selection of patients and collection of clinical data

From the Swedish Hospital Discharge Register, we identified all patients discharged from hospitals in Sweden with a diagnosis of SLE (ICD-7: 456,20; ICD-8: 734,10; ICD-9: 710A), as either a primary or a secondary diagnosis, during 1964–1995. We excluded all patients younger than 20 years at the first discharge and those who had ever been discharged with a

Abbreviations: DLBCL, diffuse large B cell lymphoma; EBV, Epstein–Barr virus; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

diagnostic code of RA, psoriatic arthritis or ankylosing spondylitis. Exclusions were also made if the patient had a discharge diagnosis of cancer before or at the first discharge.

By linking the Swedish Cancer Register with the Swedish Hospital Discharge Register, we identified 42 cases of non-Hodgkin's lymphoma (NHL) (ICD-7, ICD-8: 200, 202) among 6438 patients with SLE.

To identify risk factors of developing NHL in a SLE population, a nested case control study was performed. For each case where SLE as well as NHL diagnoses were confirmed, five controls from the SLE cohort were selected. The controls were matched for gender and were required to have an observation period free from cancer as long as or longer than the matched NHL–SLE case. The follow-up time for survival of the lymphoma cases was extended to June 2005.

From the Swedish Hospital Discharge Register, the medical records from the hospital admissions of each patient were retrieved. Every case and all but 8 control patients (10%) could be evaluated from the medical records that were obtained. The included patients had been treated in 43 different hospitals throughout Sweden. The clinical data were reviewed and evaluated with respect to whether the patients fulfilled the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE.[21] Patients not fulfilling these criteria as well as patients with incorrect diagnosis registrations were excluded. Data retrieved from the medical records also included treatment, medical events and comorbidities.

Statistics

Calculations of relative risks, with 95% confidence intervals, for each clinical/serological feature against the lymphoma outcome were performed using Statistical Packages for the Social Sciences (SPSS).

Analysis of lymphoma tissues

From the medical records, we identified code numbers of the tissue specimens on which the lymphoma diagnosis was based. The original slides and paraffin blocks were collected from 10 Swedish pathology departments. The original slides were reviewed to confirm the diagnosis of lymphoma, additional tissue sections were cut, and appropriate routine immunostainings were performed. One experienced haematopathologist (CS) blinded to all clinical data classified the lymphomas according to the recently described WHO classification.[13] Additional immunohistochemical characterisation was performed on those lymphomas diagnosed as DLBCL. Occurrence of EBV was examined by in situ hybridisation (ISH).

Subtyping of lymphoma by immunohistochemistry

A Ventana XT module (Ventana medical systems, Tucson, AZ) was used for the immunohistochemical staining procedure. Briefly, paraffin-embedded sections (4 μm thick) were deparaffinised, and all sections except for kappa and lambda antigen stainings were subjected to heat-induced antigen retrieval programmes. Primary antibodies directed against bcl-2, bcl-6, CD3, CD5, CD8, CD20, CD45, CD79a, CD138, Cyklin D1, Ki-67, kappa, lambda, TDT (Dakocytomation, Glostrup, Denmark), CD4 (Novacastra laboratories Newcastle upon Tyne, UK), CD10, CD23 (Ventana) and CD30 (Beckman Coulter, Brea CA) antigens were incubated for 30 min. An amplification kit (Ventana) was used to enhance staining for CD4, CD30, bcl-6 and cyklin D1, and the Iview DAB detection kit (Ventana) was used for stainings. Sections were counterstained with haematoxylin, with the blueing reagent kit (Ventana).

Immunostaining for CD7 (DakoCytomation), perforin, granzyme B, CD56 (Novacastra) and IRF-4 (Santa Cruz biotechnology, Santa Cruz, CA) antigens were performed manually. Following deparaffinisation of sections, heat-induced antigen retrieval was used for each antibody. Primary antibodies, secondary rabbit antimouse or rabbit antigoat (for IRF-4 antibody detection) antibodies and ABC complex were added sequentially for 30 min (DakoCytomation). Immunoreactivity was visualised with 3,3-diaminobenzidine and counterstained with Mayer's haematoxylin. All incubations were performed in room temperature. Staining results were estimated by conventional microscopy of coded slides (CS). To subclassify the DLBCLs into GC and non-GC subtypes, the same method (stainings with CD10, bcl-6, IRF-4) and cutoff values as described previously[19 20] were used. A staining result was considered positive if 30% or more of the tumour cells were stained.

In situ hybridisation for Epstein–Barr virus related RNA

ISH for Epstein–Barr virus related RNA (EBER) was performed on paraffin-embedded sections (4 μm thick) in Ventana XT module according to the manufacturer's instructions (Ventana). The study was approved by the local ethics committee at the Karolinska Institute.

RESULTS

Of the original 42 patients with NHL, 2 were excluded because of incorrect diagnosis code (tuberculosis and non-specific synovitis). Twenty-three were excluded for not fulfilling the ACR criteria for SLE. Seventeen patients fulfilled the ACR criteria for SLE, and their lymphoid tissues were subject to analysis and reclassification. One patient was excluded, since the lymphoma diagnosis could not be confirmed from the tissues that were available. The remaining 16—out of 40 (40%)—cases with SLE and NHL were included in the study. From the 80 SLE control patients, 22 had to be omitted because of an incorrect diagnosis code or because the medical records could not be found. From the remaining 58, the same proportion of SLE patients fulfilling ACR criteria as in the SLE-NHL cases remained after examination of medical records, 26 (45%).

Cases (with NHL and SLE) and controls were all women. The age at onset of SLE and at NHL diagnosis and the overall survival time from date of lymphoma diagnosis are presented in table 1. The mean age at onset of SLE for the control patients was 44 (10–70).

The lymphoma subtype according to the WHO classification is listed in table 1.

There was a striking predominance of DLBCL, recorded in 10 out of 16 cases (62%). The remaining cases were diagnosed as lymphoplasmacytic lymphoma (n = 2), unspecified high-grade B cell lymphoma (n = 2), follicular lymphoma (n = 1) and unspecified peripheral T cell lymphoma (n = 1). EBV was detected in 2 of 15 investigated cases (n = 13%).

Clinical and immunological characteristics are listed in tables 2 and 3.

Fourteen (88%) patients with SLE and NHL had signs of haematological aberration (leuco-/thrombocytopenia and or haemolytic anaemia). The time interval between the first onset of a haematological manifestation and the lymphoma diagnosis is shown in table 3. In all but one, this time span was more than 4 years, mostly considerably longer.

Besides frequent haematological aberrations, the NHL cases significantly more often than controls had sicca symptoms and/or salivary gland swellings as well as diffuse, non-infectious pulmonary infiltrates (table 2) that preceded lymphoma by several years. The last two associations are statistically significant but have to be interpreted with caution, since the absolute numbers are low.

Table 1 Clinical data, overall survival, lymphoma type and results of in situ hybridisation for EBV in lymphomas of the 16 reviewed female cases with SLE and NHL

No.	Age at SLE onset	Age at NHL diagnosis	Surviving years	Living/death age	Lymphoma type according to WHO classification	EBV-pos lymphoma
1	19	32	>11	Yes	DLBCL	No
2	22	33	>22	Yes	DLBCL	Yes
3	43	56	>11	Yes	DLBCL	No
4	54	56	<1	No/56	DLBCL	No
5	54	63	>14	Yes	DLBCL	No
6	50	66	>14	Yes	DLBCL	No
7	39	67	<1	No/67	DLBCL	No
8	69	73	<1	No/73	DLBCL	No
9	69	74	>11	No/85	DLBCL	No
10	53	82	>2	No/84	DLBCL	No
11	37	48	<1	No/48	Peripheral T cell lymphoma	No
12	44	65	<1	No/65	Unspec high-grade B cell lymphoma	No
13	15	43	<1	No/43	Unspec high-grade B cell lymphoma	Not analysed
14	61	69	>10	No/79	Follicular lymphoma	No
15	67	68	>7	No/75	Lymphoplasmacytic lymphoma	No
16	66	74	<1	No/74	Lymphoplasmacytic lymphoma	Yes
	Mean 48	Mean 61				

DLBCL, diffuse large B cell lymphoma.

In contrast, a severe prompt treatment demanding organ manifestation like glomerulonephritis was found more frequently, albeit not significantly, among the SLE controls. Immunological tests revealed an almost obligatory presence of antinuclear antibodies and/or LE cells without any difference between the NHL–SLE cases and the SLE controls, 88 and 92%, respectively.

All patients, cases as well as controls, had been treated for their SLE with oral glucocorticoids. In addition, 7 patients among the lymphoma cases had been treated with cytotoxic agents (44%), 5 with azathioprine and 2 with cyclophosphamide (table 3). Among the SLE controls, 10 out of 26 (38%) patients had been treated with cytotoxic agents.

Ever use of azathioprine (RR 0.9; 0.5 to 2.5) and cyclophosphamide (RR 1.1; 0.3 to 3.3) did not increase the risk of NHL. Symptoms that raised suspicion of a malignant process/lymphoma and Ann Arbor staging at lymphoma diagnosis are also listed in table 3, together with treatment for the lymphomas and the causes of death in the SLE cases. Fever, fatigue and often all B-symptoms, as well as changes in lymph-node swellings and other protuberances led to most of the lymphoma diagnosis. Two patients died before lymphoma treatment was started. All other patients were treated according to medical practice at the time of lymphoma diagnosis, including use of alcylating drugs, combination chemotherapy, radiation and/or surgery. The lymphoma itself or treatment-induced sepsis was in most cases the apprehended cause of death.

Survival data had a bimodal pattern. Seven of the SLE–NHL cases (44%) did not survive their first year after lymphoma diagnosis. On the other hand, the 5-year survival was good, 50%, and the 10-year survival only slightly less, 43% for all SLE

Table 2 Medical treatment and clinical characteristics of the SLE cases with NHL and the controls and the relative risk of lymphoma

	SLE patients with NHL n = 16 (%)	SLE patients: controls n = 26 (%)	RR (95% CI)
Oral glucocorticosteroids	16 (100)	26 (100)	
Cytotoxic agents	7 (43)	10 (38)	1.1 (0.5, 2,5)
Azathioprine	5 (31)	9 (35)	0.9 (0.4, 2.1)
Cyclophosphamide	2 (12)	3 (12)	1.1 (0.3, 3.3)
Malar rash	3 (19)	7 (27)	0.7 (0.3, 2.1)
Discoid rash	1 (6)	4 (15)	0.5 (0.1, 3.0)
Photosensitivity	6 (38)	7 (27)	1.3 (0.6, 2.9)
Oral ulcers	3 (19)	1 (4)	2.2 (1.1, 4.5)
Sicca symptoms and/or salivary-gland swellings	5 (31)	1 (4)	2.7 (1.5, 5.0)
Arthritis	13 (81)	21 (81)	1.0 (0.4, 2.7)
Pleuritis	12 (75)	18 (69)	1.2 (0.5, 3.0)
Recurrent pneumonias and/or pulmonary infiltrates	7 (43)	3 (12)	2.5 (1.3, 4.9)
Pericarditis	6 (38)	4 (15)	1.9 (0.9, 3.9)
Glomerulonephritis	2 (12)	6 (23)	0.6 (0.2, 2.2)
Epilepsia, psychosis, CNS vasculitis	– (0)	5 (19)	
Leucopenia	13 (81)	17 (65)	1.7 (0.6, 5.0)
Thrombocytopenia	5 (31)	10 (38)	0.8 (0.4, 1.9)
Autoimmune haemolytic anaemia	4 (25)	– (0)	3.2 (2.0, 5.0)
ANA	14 (88)	24 (92)	0.7 (0.3, 2.1)
DNA	4 (25)	16 (62)	0.4 (0.1, 1.0)
SS-A and/or SS-B	4 (25)	2 (8)	2.0 (1.0, 4.1)
Elevated IgG	9 (56)	12 (46)	1.3 (0.6, 2.8)
Coombs test positive	3 (19)	1 (4)	2.2 (1.1, 4.5)
Complement disorder	4 (25)	7 (27)	0.9 (0.4, 2.3)
False positive Wasserman reaction and/or anticardiolipin antibodies	4 (25)	2 (8)	2.0 (1.0, 4.2)

ANA, antinuclear antibodies; DNA, antibodies to native DNA; SS-A, antibodies to Ro antigens; SS-B, antibodies to La antigens.

Table 3 Clinical and immunological features and lymphoma treatment in patients with SLE and NHL

Patient no.	Clinical features of SLE In parentheses: time interval between first haematological symptom—NHL diagnosis (years)	Laboratorial and immunological features	Clinical presence of lymphoma/Ann Arbor staging at lymphoma diagnosis	Lymphoma treatment	Cause of death
1	Arthritis, malar rash, photosensitivity, salivary gland swellings, xerostomia, pulmonary infiltrates, recurrent pneumonias	ANA SS-A, SS-B IgG 31 g/l IgM 5.7 g/l	B-symptoms, cervical lymph nodes/IV	Prednimustin	–
2	Arthritis, photosensitivity, oral ulcers, pleuritis, leucopenia (4), sicca symptoms	ANA SS-A, SS-B IgG 39 g/l IgA 10 g/l	Nausea, eating problems/IV	Surgery 8 CHOP-M 5 VePAC Radiotherapy	–
3	Arthritis, pleuritis, pericarditis, pulm infiltrates, leucopenia (13)	ANA DNA IgG 20 g/l Coombs test + Compl do (C4)	Eye irritation, unilateral exoftalmus/III.1	Surgery Prednimustin	–
4	Arthritis, pleuritis, thrombocytopenia (1½), glomerulonephritis	ANA neg SS-A, SS-B Compl do (C4) Subnormal IgG	Cervical, axillar lymph nodes, Fever/III.1	9 CHVP	Lymphoma
5	Perimyocardits, pleuritis, leucopenia (10)	ANA DNA	Inch-sized protuberance in chest wall/II	4 CHOP Radiotherapy	–
6	Arthritis, malar rash, discoid rash, photosensitivity, KCS, leucopenia (15)	ANA DNA (False positive) WR IgG 30 g/l	Pathological femur fracture when walking/IV	Radiotherapy Relapse 1 year later: 8 CNOP	–
7	Arthritis, photosensitivity, malar rash, pleuritis, leucopenia, thrombocytopenia, haemolytic anaemia (21)	ANA ''Hypergamma''	Fatigue Pancytopenia/IV	Death short after lymphoma diagnosis	Lymphoma
8	Arthritis, pleuritis, pulmonary infiltrates, anaemia, leucopenia, severe immunological thrombocytopenia (4)	ANA Coombs test+ Anticardiolipin antibodies IgG 21 g/l	Swelling, pain left cheek/II	CHOP	Lymphoma (after second CHOP)
9	Arthritis, pleuritis, pleuropneumonia, leucopenia, autoimmune haemolytic anaemia (8)	ANA (False positive) WR Compl do (C4) Coombs test+ IgA 4,9 g/l	Severe abdominal pain/II	Surgery	Info Missing
10	Arthritis, recurrent pneumonias, pulmonary infiltrates, leucopenia (9)	ANA IgG 20 g/l Serume M protein	Lymphadenopatia, fever/III	Klorambucil+Prednisolone	Respiratory insufficiency, cor pulmonale
11	Arthritis, photosensitivity, oral ulcers, recid serositis	ANA DNA IgG 16 g/l	Unilateral pelvis dilatation, B-symptoms/IV	Vincristine, cerubidin, cyclophosphamide, methotrexate, cytarabine started	Ad mortem 1 month after chemotherapy start; septic shock
12	Arthritis, sicca symptoms, pleuritis, leucopenia, (4) thrombocytopenia (ITP), pulmonary infiltrates	ANA Sm, RNP SS-A IgG 40 g/l IgM 7 g/l IgA deficiency	B-symptoms/IV	8 CHOP + Etoposide start but…	…Ad mortem in clinical picture of septic chock
13	Glomerulonephritis, leucopenia, thrombocytopenia (>16), oral ulcers, pericarditis	ANA	B-symptoms, lymph nodes/III.2	8 CHOP	Ad mortem Candida sepsis
14	Photosensitivity, pleuropericarditis, KCS, leucopenia (8)	ANA (False positive) WR IgA 4,5 g/l	Impaired nose breathing, swelling/I	Radiotherapy Relapse: radiotherapy	Info Missing
15	Arthritis, pleuritis, haemolytic anaemia, leucopenia (16)	ANA IgM 24 g/l Compl do (C4)	Fever, fatigue/IV	Chlorambucil	Septicaemia (pseudomonas)
16	Arthritis, pericarditis, pleuropneumonia, pulmonary infiltrates, leucopenia (8)	LE-cells IgG 23 g/l	Fever/IV	–	Lymphoma diagnosis at autopsy

ANA, antinuclear antibodies; DNA, antibodies to native DNA; SS-A, antibodies to Ro-antigens; SS-B, antibodies to La-antigens; RNP, antibodies to U1RNP antibodies; Sm, antibodies to Sm antigens; LE-cells, pos LE cell phenomenon; WR, Wasserman reaction; Compl do (C4), Complement disorder with low C4; Ig, etc, highest measure of an elevated immunoglobulin; KCS, keratoconjunctivitis sicca; CHOP, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone. CHVP, Vinblastine instead of vincristine; VePAC, Etoposide, Prednisolone, Cytarabine, Lomustine.

patients with NHL. Two of the 10 DLBCL cases could be classified as a GC type owing to positive stainings for CD 10 or bcl-6 as well as negative staining for IR-4 (Table 4). These two patients were still alive 14 and 22 years, respectively, after lymphoma diagnosis.

DISCUSSION

The striking predominance of one specific lymphoma subtype, DLBCL, among patients with SLE confirms the previously published data from Bernatsky *et al* in their multisite international SLE cohort from 23 rheumatological centres.[12] In the general population in western countries, DLBCL constitutes 30–40% of adult NHL,[13] and in our national SLE cohort, the proportion was 62%. The presence of certain clinical SLE phenotypes including haematological manifestations, sicca symptoms/salivary gland swellings as well as pulmonary infiltrates and/or recurrent pneumonias was associated with increased risk to develop lymphoma, whereas treatment with the traditional antirheumatic, cytotoxic drugs azathioprine and cyclophosphamide was not. The prognosis in this nested case control study, a 50% 5-year overall survival after NHL diagnosis, is fairly good and comparable with the general lymphoma population—in striking contrast to previous observations in SLE patients.[12]

Treatment decisions for lymphoma are based on clinical staging. The Ann Arbor staging for lymphoma divides the tumour at diagnosis into nodal, extra nodal or disseminated disease.[22] In NHL, staging has more often been based on clinical than pathological findings. An often-used prognostic tool is the International Prognostic Index (IPI).[23] To further improve prognostication, molecular expression analysis of NHL tissue has been developed. Thus, by molecular classification using

Table 4 Immunohistochemical expression and overall survival in SLE patients with DLBCL

Patient no.	CD 10 (%)	bcl-6 (%)	IRF-4 (%)	bcl-2 (%)	Survival (years)
1	0	0	100	17	>11
2	**100**	6	0	0	>**22**
3	8	0	17	41	>11
4	0	0	0	0	<1
5	0	**42**	**18**	0	>**14**
6	0	0	95	0	>14
7	0	35	40	0	<1
8	0	0	0	0	<1
9	0	0	80	0	>11
10	0	0	15	63	2

GC subtypes are shown in bold. %, percentage of tumour cells with positive antibody staining.

cDNA micro-array analysis, DLBCL can be divided into prognostically significant subgroups with GC, activated B cell-like (ABC) or type 3 expression profiles where the GC group has a significantly better survival.[19 20] Several studies have used the immunohistochemical expression of, among others, CD 10, bcl-6, IRF-4 and bcl-2 to classify cases of DLBCL into GC or non-GC groups.[24–27] Positive staining for CD 10 as well as positive staining for bcl-6 (and IRF-4 negative) is considered indicative of superior survival in lymphoma in the general population, while the prognostic value of bcl-2 staining is still controversial.[19] By subtyping SLE patients with DLBCL into GC and non-GC subtype, we found a small proportion of patients with a better prognosis, the GC subtype, which in the general population of lymphoma patients is associated with good prognosis. Although anecdotal, this observation could indicate that this classification could also be relevant in patients with SLE who develop NHL.

Our knowledge of the aetiology and the pathogenesis of lymphoma development in rheumatic diseases is still limited. In RA, patients with the highest burden of inflammatory activity have the highest risk of lymphoma, and antirheumatic pharmacological treatment including cytotoxic agents does not seem to be a major risk factor for RA-associated lymphomas.[28 29] Similar studies have not yet been conducted in SLE patients. Each of the published studies on SLE and lymphomas contains very few lymphoma cases, and information on clinical characteristics including medical treatment is often missing.[3 4 7 9 10] Our nested case-control study is to our knowledge the largest study where clinical and laboratory findings as well as information on medical treatment are reported. From this retrospective, medical records-based study, it is hazardous to try to draw definite conclusions on clinical characteristics of SLE patients that confer a risk of developing NHL. Although our study population is small, we could still determine certain clinical features that were more frequent in the SLE patients that developed NHL. The indication of significantly more frequent involvement of mucosal membrane, salivary glands and lung parenchyma in those who developed lymphoma could imply that, in an immune-deficient individual like an SLE patient, an impaired barrier for exogenous agents, as for instance certain viruses, and recurrent infections are of importance for lymphoma transformation. We also recorded more frequently occurring haematological manifestations, both autoimmune haemolytic anaemia and leucopenia as well as hyperglobulinemia, in the cases that developed lymphoma, indicating that activation of the immune system was a risk factor of developing lymphoma

The role of EBV in the aetiology and pathogenesis of SLE has not yet been fully investigated. There are observations that EBV may act as a trigger in the development of SLE in some cases.[30] In our study, EBV was detected by ISH in the lymphoma tissue of 2 of 15 patients. Even if there are few cases, and EBV infections could not explain the elevated risk of developing NHL in SLE, a connection cannot be ruled out in these 2 individual cases.

The study period covered 1965–1995, an era when manifestations of an inflammatory systemic disease like SLE in Sweden meant hospitalising, perhaps with the exception of SLE patients with a predominating skin rash, reflected by the relatively few patients with cutaneous manifestations in our cohort. One strength of our study was that we included SLE patients from a variety of medical specialty departments, with only 8 of 16 patients with SLE and lymphoma ever seeing a rheumatologist. We therefore believe that our patients are unselected, and the data generalizable to the Swedish SLE population. The median age at onset of our SLE cases was 48 years, which is similar to other SLE cohorts from the same time period.[31]

A limitation of our study is the high dropout rate. This could be explained by rigorous exclusion procedures (strictly ACR classification criteria), resulting in missing cases, however, both among SLE-NHL cases and SLE controls. Thus, the dropouts would not affect the estimation of risk factors in established SLE cases. Validation of the diagnoses in the Swedish Hospital Discharge Register has been made in several studies with a correct ICD-code at the 4-digit level in 86% of all main discharge diagnoses.[32] There is, however, no previous report on the validity of the SLE diagnosis. Our experience from this study, and similar ones, is that the SLE diagnosis in the Swedish Hospital Discharge Register, defined as fulfilling the 1997 ACR criteria, is less specific. This may not be surprising, as the ACR criteria are classification criteria and were not developed to be diagnostic criteria for clinical practise.

The differential diagnosis of SLE versus primary Sjögren's syndrome is sometimes difficult, and the possibility of an overlap syndrome must be kept in mind. This difficulty in differentiating among the systemic autoimmune diseases has recently been discussed.[33] We have no reason to believe that patients with Sjögren's syndrome have been misclassified as SLE in our study, though the SLE diagnosis in our 16 lymphoma cases was well founded (table 3). On the other hand, there are several patients with a clinical and laboratory profile consistent with Sjögren's syndrome as well. Thus, some of our patients presented signs of autoimmune inflammatory disease with a possible overlap of SLE and Sjögren's syndrome; those were among the SLE patients with the highest risk of developing lymphoma in our cohort.

In conclusion, the most common subtype of lymphoma in SLE patients is DLBCL. Certain clinical features seem to confer risk factors to develop lymphoma, including haematological manifestations, Sjögren-like disease and pulmonary involvement

The use of immunosuppressive drugs was not substantial in our cohort of SLE cases with lymphoma arguing against treatment-induced lymphoma. Immunohistochemical analysis

for subtyping of DLBCLs to predict prognosis seems to be applicable also for patients with SLE and lymphoma but needs confirming on a larger scale. Clinicians caring for SLE patients should keep the lymphoma risk in mind and regularly check for lymphadenopathy.

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