Clinical characteristics and risk factors associated with lymphoma in patients with systemic lupus erythematosus: a nationwide cohort study.

María Martín-López[1], María Galindo-Izquierdo[1], José M. Pego-Reigosa[2], Norman Jiménez[3], Alejandro Olivé[4], Eva Tomero[5], Mercedes Freire[6], Julia Martínez-Barrio[7], Alina Boteanu[8], Eva Salgado[9], Antonio Fernández-Nebro[10], Jaime Calvo-Alén[11], Raúl Menor-Almagro[12], Iñigo Rúa-Figueroa[13]

[1]Rheumatology Department , Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (imas12), Madrid, Spain; [2]Rheumatology Department, Hospital do Meixoeiro, Vigo, Galicia, Spain; [3]IRIDIS Group (Investigation in Rheumatology and Immune-Diseases), Galicia Sur Health Research Institute (IISGS), Spain; [4]Rheumatology Department, Hospital Universitario Germans Trías i Pujol, Badalona, Spain; [5]Rheumatology Department, Hospital Universitario La Princesa, Madrid, Spain; [6]Rheumatology Department, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; [7]Rheumatology Department, Hospital Universitario Gregorio Marañón, Madrid, Spain; [8]Rheumatology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain; [9]Rheumatology Department, Complejo Hospitalario de Orense, Orense, Galicia, Spain; [10]Rheumatology Department, Hospital Regional Universitario de Málaga, Málaga, Spain; [11]Rheumatology Department, Hospital Universitario de Araba, Vitoria, Spain; [12]Rheumatology Department, Hospital de Jerez, Cádiz, Spain; [13]Rheumatology Department, Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas de Gran Canaria, Spain.

Corresponding author: María Martín-López, MD. ORCiD iD: 0000-0002-4218-5731. Rheumatology Department, Hospital Universitario 12 de Octubre, Centro de Actividades Ambulatorias. Avda. de Córdoba, s/n. Postal code 28041. Madrid, Spain. E-mail address: marymartin12@hotmail.com

ABSTRACT

Objectives: We performed a study tTo assess the characteristics and risk of lymphoma in a large cohort of patients with systemic lupus erythematosus (SLE).

Methods: We performed case-cohort analyses within a dynamic cohort of SLE patients from the Spanish Society of Rheumatology Lupus Registry (RELESSER). Clinical and analytical features were compared between the lymphoma SLE group and the control SLE group using an independent-sample *t* test or Mann-Whitney test for continuous variables and the chi-square test for categorical variables with the Fisher exact test if necessary. The multivariate analysis was based on a generalized linear model.

Results: We studied 21 patients with SLE and lymphoma and 3,965 non-lymphoma controls with SLE. Most lymphomas were of B-cell origin (n=15/21), with diffuse large B-cell lymphoma being the most frequent histological type (8/21, 38.1%). As in the general population, the risk of lymphoma in SLE was higher in male than in female patients and increased with age. In the lymphoma SLE group, bivariate analysis showed a significantly higher percentage of pericarditis, organic brain syndrome, seizures, vasculitis, hemolytic anemia, splenomegaly, venous thrombosis, and mean modified (excluding lymphoma) SLICC/ACR damage index. In contrast, renal involvement, positive anti-dsDNA, and antimalarials ever used were less frequent. Multivariate analysis confirmed that antimalarials could protect against lymphoma (OR 0.27, 95% CI 0.11–0.7; p=0.009).

Conclusions: In this large multicenter Spanish cohort, we identified characteristics of SLE that are associated with a higher risk of lymphoma. Antimalarials were significantly negatively associated with risk of lymphoma in SLE patients. Nevertheless, further prospective studies are needed to clarify these findings.

KEY MESSAGES:

- The association between lymphoma and SLE is well established, although ~~but~~ the risk factors remain unclear.
- We found a higher prevalence of comorbidities, pericarditis, hematological abnormalities, and seizure in the lymphoma SLE group.
- Antimalarials were significantly negatively associated with risk of lymphoma in SLE patients.

KEY WORDS: Lymphoma, Systemic lupus erythematosus, Cohort study, Hematological malignancies, Prognostic factors.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with a complex genetic basis. It can present with a wide range of clinical and analytical manifestations involving multiple organ systems, with heterogeneity being one of its main characteristics. Both prognosis and survival rates for SLE patients have improved in recent decades owing to meticulous early diagnosis and advances in treatment **[1-3]**. Consequently, increased survival has led to a greater incidence of long-term complications, cardiovascular disease, infections, and malignant processes, all of which affect the morbidity and mortality of patients with SLE **[4-6]**.

In this respect, dysregulation of the immune system and chronic inflammation are both recognized as ~~promoters~~ causes of malignancy **[7]**. Numerous studies have demonstrated that SLE patients have a higher overall cancer risk than the general healthy age- and sex-matched population, especially for hematological malignancies, in particular non-Hodgkin lymphoma (NHL) **[8-14]**. However, the magnitude of this increased risk is controversial. In their pivotal multicenter study from 2005, Bernatsky et al. **[8]** analyzed 9,547 SLE patients and found an estimated standardized incidence ratio (SIR) for NHL of 3.64 (95% confidence interval [CI] 2.63-4.3). In 2014, the results of a meta-analysis ~~published~~ by Apor et al. **[10]** ~~found~~ revealed an estimated SIR for NHL of 5.7 (95% CI 3.6-9.1), while a large recent meta-analysis of 24 studies dating from 1992 to 2018 reported a significantly increased SIR of 4.93 (95% CI 3.81-6.36) for NHL and 2.60 (95% CI 2.14-3.17) for Hodgkin lymphoma **[11]**.

Despite the evidence of an increased risk of lymphoma in SLE patients, the causal pathogenic mechanisms involved remain unclear, although the factors that could contribute to the increased cancer risk in SLE include treatment, a persistently activated immune system, viral infection, and overlap syndromes, as well as the greater prevalence of traditional lifestyle cancer risk factors **[12, 15-18]**. The role of immunosuppressive therapies and disease activity in the development of cancer in SLE patients ~~remains~~is controversial **[19]**. A possible ~~trend~~association has been suggested between exposure to cyclophosphamide and cumulative steroid use and the subsequent development of lymphoma **[20, 21]**, although further studies are needed for confirmation. Based on current knowledge in this area, we hypothesized that risk factors inherent to SLE or medication can increase the incidence of lymphoproliferative disorders in affected patients.

Our objective was to analyze the risk factors associated with lymphoma in patients with SLE from the RELESSER lupus registry. The secondary objectives were to characterize cases of lymphoma by histological type and location and to determine their relationship with Epstein-Barr virus (EBV), treatment, and outcome.

PATIENTS AND METHODS

Patient selection

This case-cohort study included patients aged ≥ 16 years from the RELESSER registry classified ~~with~~ as having SLE according to the revised 1997 criteria of the American College of Rheumatology (ACR) for SLE **[22~~19~~]**. RELESSER (TRANS) is a multicenter, hospital-based registry that retrospectively collects data from a large representative sample of adult patients with SLE cared for in Spanish rheumatology departments **[23~~20~~].** The exclusion criteria were meeting fewer than 4 of the 1997 ACR diagnostic criteria, loss to follow-up, and/or > 50% of data missing. Patients with a concomitant diagnosis of rheumatoid arthritis, Sjögren's syndrome, inflammatory myopathy, autoimmune hepatitis, or primary biliary cholangitis were defined as having overlap syndrome. A diagnosis of ~~l~~Lymphoproliferative disorders ~~were diagnosed by histological confirmation~~was confirmed by histopathology, and only those cases diagnosed after entry into the lupus cohort at each center were included.

In order to facilitate the analysis, participants were assigned to a cancer group and control group according to the type of lymphoma.

Data collection

The RELESSER registry includes the following data: 1) demographics; 2) age; 3) general clinical data; 4) cumulative manifestations of SLE defined according to the ACR criteria for classification of SLE and damage indexes; 5) comorbidities; 6) laboratory testing; 7) imaging or histological evidence when needed; and 8) treatment. We calculated the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index, which was modified by excluding the presence of lymphoma from the malignancy item.

The electronic medical record of each patient was reviewed, as were physical clinical reports, if ~~needed~~necessary.

We also recorded concomitant diagnoses such as antiphospholipid syndrome (Sydney criteria **[24~~21~~]**) and Sjögren's syndrome~~, —~~defined as the presence of compatible sicca syndrome and a positive Schirmer test result—which were confirmed~~, or~~ by biopsy or salivary gland scintigraphy **[25~~22~~]**.

Information on the use of corticosteroids, antimalarial drugs, and immunosuppressive therapy was also studied. Drugs were treated categorically (ever/never), although the start date of these treatments is unknown in the retrospective stage of the RELESSER registry. To avoid the bias that could be involved in analyzing the treatments included, and given that we did not know whether they were started before or after the diagnosis of lymphoma, only the use of antimalarials was analyzed, since this drug group is generally introduced from the onset of SLE.

The diagnosis of lymphoma was confirmed histopathologically. In the case of patients who developed lymphoproliferative disorders, we collected data related to lymphoma, such as the date of diagnosis, location, and histological type, EBV viral load if available, treatment received and its duration, and subsequent outcome (remission, relapse, or death).

Ethical aspects

The project complies with the principles of the Declaration of Helsinki **[26~~23~~]** and the Oviedo Convention **[27~~24~~]**. The project is included within the RELESSER registry of the Spanish Society of Rheumatology (SER) **[23~~20~~]**, which was approved by the Clinical Research Ethics Committee of Hospital Dr. Negrín.

Statistical analysis

Summary statistics were computed for continuous measures as mean ± SD or median (IQR) ~~if~~ in the case of a nonnormal distribution~~not normally distributed~~. For categorical variables, the frequency and proportion (%) were calculated. Normality was assessed using the Kolmogorov-Smirnov test. Quantitative variables were analyzed using the *t* test for independent variables or the Mann-Whitney test; categorical variables were analyzed using the χ^2 test with the Fisher exact test if necessary. The multivariate analysis was performed based on a generalized linear model, which allows the response variable (development of lymphoma) to have an error distribution other than a normal distribution. A binomial link function is used to relate the explanatory variables and the expectation of the response variable. The model only included those variables that reached $p < 0.05$ in the bivariate analysis, and the best model was selected using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The results were expressed as the odds ratio (OR) with its 95% CI.

Statistical significance was set at $p < 0.05$. Data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

A total of 3,986 patients diagnosed with SLE from the RELESSER-TRANS cohort were recruited into this study. Only 21 also had a lymphoproliferative disorder diagnosed after entry into the lupus cohort, while the remaining 3,965 were lymphoma-free. Median time from the SLE diagnosis in the control group was 9.7 (5-16) years, and the m~~M~~edian time to development of lymphoma after diagnosis of SLE was 9 (6-22) years. As expected, diffuse large B-cell lymphoma (DLBCL) was the most common diagnosis (8 patients, 38%). The chemotherapy regimens in

decreasing order of frequency were as follows: rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), 7 patients, of whom 2 also required other chemotherapy regimens and 1 radiotherapy; ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), 4 patients; DRC (dexamethasone, rituximab and cyclophosphamide), 2 patients; MATRIX (methotrexate, cytarabine, rituximab, and thiotepa), 3 patients; and VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin), 1 patient. Median duration of treatment was 6 (4-12) months. Most lymphomas went into remission (84%). Three patients relapsed (median time to relapse, 12 [8-24] months), and 4 died during follow-up. Further details on these 21 lymphoma patients are presented in Table 1.

Relationship between risk of lymphoma and SLE

To analyze the risk factors associated with lymphoma in patients with SLE, we studied sociodemographic variables, clinical and analytical features of SLE, presence of ~~other~~ concomitant rheumatic diseases, treatment received, and organ damage (modified SLICC/ACR damage index, excluding lymphoma) **[28~~25~~]**.

The bivariate analysis revealed more males in the lymphoma SLE group than in the control SLE group. Patients in the lymphoma SLE group were also older, had been diagnosed with SLE at a more advanced age, and had a higher prevalence of comorbidities (Table 2). In terms of manifestations of SLE, arthritis (71%) was mo~~st~~re common in the lymphoma SLE group. Lymphoma patients were also ~~had~~ characterized by significantly less frequent renal involvement and a higher percentage of pericarditis, vasculitis, hemolytic anemia, splenomegaly, organic brain syndrome, and seizures (Table 3).

No significant differences were observed between the 2 groups for ~~the~~ positive ~~rate~~ values of antinuclear antibodies and other auto-antibodies, except for anti-dsDNA, which were more frequently detected in the control SLE group. Eight patients had coexisting antiphospholipid syndrome and 4 had Sjögren's syndrome. ~~The prevalence of v~~Venous thrombosis was significantly ~~higher~~ more prevalent in the lymphoma SLE group, whereas arterial thrombosis, while prevalent, ~~did not reach~~was not statistically significant~~ce~~ (Table 4).

As for SLE therapy at diagnosis of lymphoma, our analysis focused only on antimalarial agents~~,~~ because the start date of the SLE therapy used in our cohort is unknown in the retrospective stage of the RELESSER registry. We ~~have~~ analyzed antimalarials because they are usually started at the onset of SLE and we ~~guessed/~~assumed~~?~~ that their use ~~is~~was prior to the diagnosis of lymphoma. Administration of antimalarials was significantly less frequent in SLE patients with lymphoma (55%) than in the control~~s group~~ (82%) (p = 0.0048).

Finally, the mean modified SLICC/ACR damage index was significantly higher in the lymphoma SLE group than in the control SLE group (2 ± 2.2 *vs* 1.1 ± 1.7, respectively; $p = 0.012$). Significant differences for patients' characteristics with respect to the modified SLICC/ACR damage index in both groups are shown in Table 5 ($p < 0.05$). All non-significant variables are presented in Supplementary material Table S1.

The multivariate analysis of the factors associated with the incidence of lymphoma in the SLE cohort was performed using a general linear model approach, and the final model showed that pericarditis, seizures, and hypertension were associated with a greater risk of lymphoma in SLE patients. Antimalarials and presence of anti-dsDNA were negatively associated with a greater risk of lymphoma (Table 6).

DISCUSSION

The spectrum of malignant tumors in SLE patients is variable, although the disease has commonly been associated with hematologic malignancies, mainly NHL. The many links between SLE and lymphoma that have been hypothesized include a shared genetic predisposition, chronic stimulation of the immune system, and disproportionate immune responses **[7, 14]**. Nevertheless, ~~although~~ the etiology of the increased risk of hematologic malignancies in patients with SLE remains unclear. We therefore performed a nationwide cohort study to characterize all patients who were diagnosed with lymphoma after a diagnosis of SLE and found that DLBCL was the most frequent histological type. Affected patients mostly presented with extranodal disease and had relatively good outcomes, probably owing to the increased clinical care they received for their SLE and earlier diagnosis. Testing for EBV (viral load or tissue) was negative in most patients, as reported elsewhere **[29~~26~~, 30~~27~~]**, although few underwent EBV testing in our sample. In any case, a potential role for EBV in lymphoma cannot be excluded, since case reports point to the occurrence of EBV-positive lymphoproliferative lesions during immunosuppressive treatment in patients affected by autoimmune disease, with spontaneous regression of lymphoma once immunosuppressive drugs have been discontinued **[31~~28~~].**

Among studies in SLE, Pettersson et al. **[32~~29~~]** observed that patients who developed SLE at an older age were more susceptible to malignancy. We observed a similar trend and found that the risk of lymphoma was higher in male than in female patients, as seen in the general population. In contrast to some studies, which found lymphoma to occur earlier in the course of SLE follow-up care **[8, 33~~30~~]**, we found the median duration of SLE ~~was~~ to be 9 years before the development of lymphoma ~~in our cohort~~.

While the association between lymphoma and SLE is well established, the risk factors involved in this association remain unclear. In this sense, we found a higher prevalence of comorbidities (hypertension, diabetes), pericarditis, hematological abnormalities (hemolytic anemia and splenomegaly), and seizure in the lymphoma SLE group than in the controls. Hematological manifestations in particular have also been seen in other cohorts **[29~~26~~, 34~~31~~, 35~~32~~]**. Furthermore, we observed that renal involvement, positive anti-dsDNA, and antimalarial drugs were significantly negatively associated with risk of lymphoma in SLE patients.

~~Importantly, our multivariate analysis also revealed the potential protective role of antimalarials in lymphoma.~~ Hydroxychloroquine is widely used in the treatment of SLE. Besides its well-established effects on skin and joint symptoms, several studies have indicated that hydroxychloroquine has relevant long-term effects in SLE, including reduced long-term damage accrual and decreased long-term mortality **[36~~33~~, 37~~34~~]**. There is also evidence supporting the association between antimalarials and lower risk of cancer in SLE patients **[~~35~~20, 38, 39~~ 37~~]**.

~~The role of immunosuppressive therapies and disease activity in the development of cancer in SLE patients remains controversial **[38]**. A possible trend has been suggested between exposure to cyclophosphamide and cumulative steroid use and the subsequent development of lymphoma **[36, 39]**, although further studies are needed for confirmation.~~ We did not analyze ~~either~~ SLE disease activity or the possible role of immunosuppressive therapies in the development of lymphoma in SLE patients, since the start dates for therapy were not recorded ~~this trend owing to the lack of information on dates of initiation of therapy~~ in the RELESSER registry. However, the mean modified SLICC/ACR damage index was 2 in the lymphoma SLE group (*vs* 1.1 in the controls), which could reflect higher SLE activity over the years preceding the diagnosis of lymphoma. This index is similar to the levels of damage found in larger SLE cohorts **[30~~27~~, 21~~39~~]** and may indicate that damage is one of several factors involved in lymphomagenesis.

This Our study has several limitations, one of which includes is its retrospective nature. Since data were collected from the RELESSER registry, information is lacking for specific cases. The measurement of disease activity and the date of initiation of treatment were not collected, and thus preventing us from studying~~we were unable to study~~ their association with the risk of lymphoma. In addition, given the limited number of lymphoma patients available for study, our statistical analysis was unable to confirm definitive associated risk factors could not be confirmed with our statistical analysis. However, our hope is that this descriptive report and the results from our large nationwide cohort will yield possible risk factors that could be further explored.

In summary, we identified a population of patients with lymphoma and SLE in a nationwide cohort. Our data suggest that some features of SLE may be associated with the development of lymphoma and that there could be a possible beneficial role for hydroxychloroquine in the prevention of lymphoma in patients with SLE. Our hypothesis needs to be confirmed in larger-scale prospective studies. Analysis of the prospective stage of RELESSER will increase our knowledge of this area.

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