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Research Article

Development of lymphoma in patients with primary Sjögren syndromes

Schenone LN[1], Pellet AC[1], Mamani M[1], Melo F[1], Adrover M[1], Barreira J[2], Dermarchi J[2], Escobar CS[2], Santiago L[3], Salvatierra G[4], Nitsche A[5], Asnal C[5], Amitrano C[5], Pucci P[5], Crow C[5], Ratti L[6], Cruzat V[6], Papasidero S[7], Caeiro F[8], Retamozo S[8], Saurit V[8], Baenas D[8], Riscanevo N[9], Gobbi C[9], Albiero E[9], Vélez S[10], Juarez V[11] & Secco A*[1]

[1]Rheumatology Unit, Hospital Bernardino Rivadavia, Buenos Aires, Argentina

[2]Rheumatology Unit, Hospital Británico, Buenos Aires, Argentina

[3]Rheumatology Unit, Organización Médica de Investigación, Buenos Aires, Argentina

[4]Rheumatology Unit, IPRI, Santiago del Estero, Argentina

[5]Rheumatology Unit, Hospital Alemán, Buenos Aires, Argentina

[6]Rheumatology Unit, Clinica Bessone, Buenos Aires, Argentina

[7]Rheumatology Unit, Hospital Tornu, Buenos Aires, Argentina

[8]Rheumatology Unit, Hospital Privado Universitario de Córdoba, Córdoba, Argentina

[9]Rheumatology Unit, Hospital Córdoba/ Sanatorio Allende Córdoba, Córdoba, Argentina

[10]Rheumatology care offices, Buenos Aires, Argentina

[11]Rheumatology Unit, Hospital del Milagro, Salta, Argentina

*Author for correspondence:

anastasiasecco@gmail.com

Background: Lymphoma is the main complication of primary Sjögren syndrome (pSS). The aim of this study was to describe the prevalence and incidence rate of lymphoma in patients with pSS in eleven centers in Argentina. To determine the frequency of commitment of the domains of the baseline clinical ESSDAI in the patients who developed lymphoma in the course of their follow-up and compare it with the rest of the sample.

Methods and findings: We included patients older than 18 years with a diagnosis of pSS according to American College of Rheumatology/European League against Rheumatism (ACR/EULAR)2002/2016 criteria, included in a multi-center Argentine database. Patients diagnosed with another associated autoimmune rheumatic disease were excluded. Six hundred and eighty one patients were included, 95% female, with a mean age of 54.41 years (± 13.70). Sixteen patients presented lymphoma (prevalence: 2.35%, 95% CI: 1.2-3.4%). The average follow-up time was 4.7 years (± 4.94). Six hundread and thirty three patients contributed data for the survival analysis. The incidence rate of lymphoma was 0.54 per 100 patient-years (95% CI: -0,26 a 1,34). The most frequently lymphoma type was MALT. Patients who developed lymphoma had a higher frequency of involvement of most of the domains of the baseline clinical ESSDAI compared to patients who did not present this complication, observing statistically significant differences in glandular (68,75% *vs* 28.69%, p:0,001), and cutaneous (31.25% *vs* 10.99%, p: 0.01) domains. The glandular domain of clinical ESSDAI was the main domain associated lymphoma development (H.R: 4.54, 95% CI: 1.57-13.12).

Conclusion: This was the first study with data on the population of Argentina about the prevalence of lymphoma in patients diagnosed with Sjogren's syndrome. The prevalence of lymphoma in our cohort was lower than previously published. Despite observing a lower frequency of lymphoma in our study, we found an association with risk markers described in the literature, such as baseline parotidomegaly and cutaneous involvement.

Keywords: lymphoma • Sjögren • cancer • parotidomegaly

Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune systemic disease that presents a wide variety of manifestations. The dryness of mucous membranes is one of the main findings, however, many patients can develop extraglandular compromise of different domains such as the musculoskeletal and/or the involvement of internal organs such as kidneys and lungs, among others [1,2]. It is classified as type I and type II, the former being the one with the greatest association to oncohematological complications, mainly lymphoma. The presence of recurrent parotidomegaly, decrease in complement, especially C4, the presence of positive cryoglobulins, positive rheumatoid factor and cutaneous vasculitis, among others, have been described as predictors of its appearance [3-5]. The presence of positive rheumatoid factor in serum has been described as an independent risk factor for the development of lymphoma in patients with pSS [6]. The role of the presence of germinal centers in minor salivary gland biopsy as a predictor of lymphoma is still controversial [7-11].

Non-Hodgkin's Lymphoma (NHL) is one of the most feared complications of pSS. The most frequent is MALT-type lymphoma, with localization in the parotid glands being common. The determination of those patients with greater risk for the development of these neoplasms would allow an adequate and strict clinical monitoring to ensure the early diagnosis of this complication [11-14].

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is a clinimetric tool that evaluates systemic activity in patients with pSS. It was developed by an international group of experts and contains 12 domains. It is a widely validated index, highly reproducible and sensitive to detect changes [15]. The activity of the disease measured by ESSDAI is an independent marker for the turn to lymphoma in patients with pSS [6].

In part due to the lack of accessibility of the complementary laboratory methods in all the care areas, the Clinical EULAR Sjögren's Syndrome Disease Activity Index (ClinESSDAI) was developed, which consists of a simplified version of the ESSDAI that does not include the biological domain of the ESSDAI [16]. A study

carried out by Quartuccio et al. in an Italian cohort of patients with pSS showed that there is a correct correlation between both clinimetric tools, ESSDAI and clinESSDAI [17]. On the other hand, a multicentric study published in 2014 showed the correlation with the severity of the activity of the disease with the scales reported by the patients [18].

There are no multicenter data in the Argentine population regarding the appearance of lymphomas in patients with pSS and their possible clinical manifestations associated with the development of this neoplasma. The aims of this study were to describe the prevalence and incidence rate of lymphoma in patients with pSS in eleven centers in Argentina, to determine the frequency of commitment of the domains of the baseline clinical ESSDAI in the patients who developed lymphoma in the course of their follow-up and to compare it with the rest of the sample.

Materials and methods

Population and sample

We included patients older than 18 years with a diagnosis of pSS according to ACR-EULAR 2002/2016 criteria, included in the GESSAR database. Patients diagnosed with another associated autoimmune rheumatic disease were excluded.

Design

To respond to the primary objective, the design is observational and descriptive. To respond the secondary objective is observational, analytical and retrospective cohort.

Data recollection

The multi-center database GESSAR was used, which has as a primary objective to estimate the frequency of glandular and extraglandular manifestations of SSp in population Latin American and, in addition, estimate the percentage of patients with SSp type I and type II. This base was elaborated with the advice of national and international professionals, with extensive experience in SS. The registration and storage of data is carried out in electronic format through an application computing. This application contains filters and dialogs of help to optimize the reliability of the data. Participate in it, doctors belonging to specialized centers in rheumatology, both public and private, from different provinces of the country. To be included, patients must meet the American-European criteria 2002 for SSp and being under active monitoring by the doctor handler. The data of all the manifestations secondary to the disease that the patient presents during the course of it, and every 12 months, are updated, incorporating the new manifestations that have emerged in the course of that lapse of time. Patients must sign their informed consent prior to the inclusion of information. The base is incorporated to the National Registry of Protection of Personal Data.

Ethical repairs

The GESSAR multicenter database is approved by an independent Ethics Committee and subject to the rules international research Helsinki Association World Medical. Patients must grant and sign a consent informed prior to the inclusion of their data in base.

Analysis

For descriptive statistics, continuous variables were reported as mean and standard deviation, and categorical variables as proportions. The number of events (lymphoma) per 100 patients / year was calculated. To compare if the frequency of commitment of each ESSDAI basal domain was higher in the patients who developed lymphoma than in those who did not present this complication, Chi2 or Fisher's exact test was used, according to the expected frequency distribution table. For the evaluation of the independent association of each clinical domain of ESSDAI with lymphoma, Cox regression analysis was performed, adjusted by sex, age and laboratory parameters associated with the development of lymphoma (C4, cryoglobulins, C3, rheumatoid factor, gammaglobulins).

Results

We included 681 patients, 95% female, with a mean age of 54.41 years (SD ± 13.70), mean age at diagnosis of 49.73 years (SD ± 13.45) and mean age of onset of symptoms of 47.19 years (SD ± 13.03). The general characteristics of the cohort are described in Table 1.

Sixteen patients presented lymphoma (prevalence: 2.35%, 95% CI: 1.2-3.4%). The average follow-up time was 4.7 years (SD ± 4.94). Six hundred and thirty-three patients provided data for the survival analysis. The incidence rate of lymphoma was 0.54 per 100 patient-years (95% CI: -0, 26-1,34). The median time from the diagnosis of pSS to the development of lymphoma was 4.4 years (SD ± 4.10). The most frequently encountered type was MALT. When

Table 1. General characteristics of the cohort.	
Cohort (n: 681)	**General characteristics**
Sex (female %)	95%
Age (m, SD)	54.41 years (+/- 13.70)
Age at diagnosis (m, SD)	49.73 years (+/- 13.45)
Age of onset of symptoms (m, SD)	47.19 years (+/- 13.03)
Follow-up time (m, SD)	4.7 years (+/- 4.94)
Schirmer test (%)	92.12%
Rose bengal, green lysamine or ocular staining score (%)	64.92%
Sialometry (n: 247. %)	81.38%
Anti Ro+ (%)	68.90%
Anti La+ (%)	38.73%
Salivary gland biopsy + (n: 357. %)	84%
m: mean. SD: standard deviation	

Table 2. Baseline clinical ESSDAI (entire cohort).			
Domain	**Lymphoma n=16 (%)**	**No Lymphoma n=665 (%)**	**p-value**
Glandular	68.75	28.69	0.001
Articular	81.25	71.84	0.576
Cutaneous	31.25	10.99	0.012
Respiratory	37.5	18.26	0.051
Renal	0	3.53	1
Pns	0	10.53	0.394
Cns	0	6.27	0.616
Muscular	7.69	1.58	0.204
Hematological	35.71	26	0.415

comparing the frequency of commitment of each domain in the baseline assessment between the patients who developed lymphoma versus those of the entire population included in the study, a significantly higher frequency of involvement in the glandular and cutaneous domain was observed (Table 2). Similar results were observed when analyzing only the 633 patients who provided information for the survival analysis (Table 3).

The glandular domain of clinical ESSDAI was the main domain associated with lymphoma development (H.R: 4.54, 95% CI: 1.57-13.12). However, after adjusted by sex, age and laboratory parameters associated with the development of lymphoma (C4, cryoglobulins, C3, rheumatoid factor, gammaglobulins), in the Cox regression analysis, muscular domain and C4 variables presented a confusing effect with parotid swelling. Results can be seen in Table 4.

Despite observing a lower frequency of lymphoma in our study, we found an association with risk markers described in the literature, such as baseline parotidomegaly and cutaneous involvement.

Discussion

The relationship between pSS and the development of lymphoma was described for the first time more than 50 years ago and to date numerous studies have been carried out that have confirmed the risk of development in patients with the disease [19,20].

It is known that autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis as well as pSS present an increased risk of lymphoma, however to date most of the published studies show that the greatest association occurs in patients with pSS [14,21-24]. Kovács et al. published a study in 2010 in which he analyzed the different tumors presented by patients with pSS, finding lymphomas in first place, with a prevalence of 5% [25]. A cohort study conducted in Sweden

Table 3. Baseline clinical ESSDAI (patients who provided information for the survival analysis).			
Domain	**Lymphoma n=16 (%)**	**No Lymphoma n=617 (%)**	**p-value**
Glandular	68.75	28.72	0.001
Articular	81.25	72.92	0.458
Cutaneous	31.25	10.8	0.011
Respiratory	37.5	18.63	0.058
Renal	0	3.62	0.439
Pns	0	11.11	0.158
Cns	0	6.55	0.29
Muscular	7.69	1.65	0.105
Hematological	35.71	26.9	0.465

Table 4. Cox regression analysis.		
Domain	**HR**	**CI95%**
Glandular Domain	1.68	0.47- 6.05
Muscular Domain	6.27	0.76- 51.57
C4 Decrease	3.01	0.83-10.89

in 2006 demonstrated a 16-fold increased risk of developing lymphoma in patients with pSS [14]. A meta-analysis and systematic review published by Nishishinya et al confirms the prevalence of 5% lymphoma in patients with pSS [11,26-28]. We found in our analysis a lower prevalence than previously reported in the literature.

To date there is little information about the basal activity of the disease and the risk of developing lymphoma. Nocturne et al published a study that demonstrated the independent association of activity of the disease with the development of lymphoma in patients with pSS [6]. A Spanish cohort of 1045 cases with pSS was studied by Brito-Zerón et al. with the aim of determining the survival of the patients and to strap it with the baseline ESSDAI. This group showed that patients with pSS who, at the time of diagnosis, had an activity value of ESSDAI equal to or greater than 14 had a lower survival. Risselada et al published a study, which showed that the baseline accumulated activity by ESSDAI is associated with a worse prognosis and a more severe disease with treatment failure [15,16,29-31]. In our study, only a statistically significant association was shown for the lymphoma shift in patients with pSS who presented baseline parotidomegaly and cutaneous involvement evaluated by ESSDAI, despite having found compromise in other domains as well. However, our findings correlate with those previously published about the marked relationship between the commitment of the glandular domain of the ESSDAI and the skin involvement and the risk of conversion to lymphoma [3-5,31].

We consider a limitation of our study the relative short period of follow-up, the lack of results of the total score of the clinical ESSDAI and incomplete data of results of C3, C4 and, especially, cryoglobulins. The long-term follow-up of patients with pSS as well as the greater diffusion and knowledge of the clinimetric tools will offer us more information about the behavior of the disease, which will encourage the development of new drugs and therapeutic tools in the future to treat this intriguing pathology.

Conclusion

This was the first study with data on the population of Argentina about the prevalence of lymphoma in patients diagnosed with pSS. The prevalence of lymphoma in our cohort was lower than previously published, which is between 4 to 6%. Despite observing a lower frequency of lymphoma in our study, we found an association with risk markers described in the literature, such as baseline parotidomegaly and cutaneous involvement.

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