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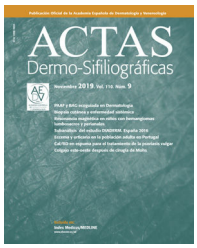

ORIGINAL ARTICLE

[Translated article] Primary Cutaneous Lymphoma Registry of the Spanish Academy of Dermatology and Venereology (AEDV): Data for the First 5 Years

D. Falkenhain-López[a,*], C. Muniesa[b], M.T. Estrach[c], M. Morillo-Andújar[d], Y. Peñate[e], E. Acebo[f], R.M. Pujol[g], M.P. García-Muret[h], S. Machan[i], S. Medina[j], R. Botella-Estrada[k], R. Fernández de Misa[l], M. Blanes[m], A. Flórez[n], G. Pérez-Paredes[o], R. Izu[p], I. Yanguas[q], E. Silva-Díaz[r], A. Pérez-Ferriols[s], L. Prieto-Torres[t], A. Zayas[u], M.E. Parera-Amer[v], A. Pérez[w], L. Aspe[x], C. Román[y], M.P. Sánchez-Caminero[z], J. Bassas-Vila[aa], J.D. Domínguez-Auñón[ab], L. Calzado[ac], M. Navedo[ad], A. Ortiz-Prieto[ae], O. Servitje[b], I. Polo-Rodríguez[j], I. Torres[k], M.N. Hernández-Hernández[l], J. Mitxelena-Eceiza[q], A. García-Vázquez[r], I. García-Doval[af,ag], P.L. Ortiz-Romero[a]

[a] *Departamento de Dermatología, Hospital Universitario 12 de Octubre, Madrid, Spain*
[b] *Departamento de Dermatología, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*
[c] *Departamento de Dermatología, Hospital Clínico, IDIBAPS, Universitario de Barcelona, Barcelona, Spain*
[d] *Departamento de Dermatología, Hospital Virgen del Rocío, Sevilla, Spain*
[e] *Departamento de Dermatología, Complejo Hospitalario Universitario Insular Materno-Infantil, Gran Canaria, Spain*
[f] *Departamento de Dermatología, Hospital Universitario de Cruces, Barakaldo, Bizkaia, Spain*
[g] *Departamento de Dermatología, Hospital del Mar, Barcelona, Spain*
[h] *Departamento de Dermatología, Hospital Santa Creu i Sant Pau, UAB Barcelona, Barcelona, Spain*
[i] *Departamento de Dermatología, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain*
[j] *Departamento de Dermatología, Hospital Universitario Príncipe de Asturias, Madrid, Spain*
[k] *Departamento de Dermatología, Hospital Universitario La Fe, Valencia, Spain*
[l] *Departamento de Dermatología, Hospital Universitario Nuestra Señora de la Candelaria, Tenerife, Spain*
[m] *Departamento de Dermatología, Hospital General Universitario de Alicante, Alicante, Spain*
[n] *Departamento de Dermatología, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain*
[o] *Departamento de Dermatología, Hospital Universitario Marqués de Valdecilla, Santander Cantabria, Spain*
[p] *Departamento de Dermatología, Hospital Universitario de Basurto, Bilbao, Bizkaia, Spain*
[q] *Departamento de Dermatología Complejo Hospitalario de Navarra, Navarra, Spain*
[r] *Departamento de Dermatología, Hospital Clínico Universitario de Valencia, Valencia, Spain*
[s] *Departamento de Dermatología, Hospital General Universitario de Valencia, Valencia, Spain*
[t] *Departamento de Dermatología, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain*

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* Corresponding author.
E-mail address: danifalkenhain@gmail.com (D. Falkenhain-López).

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[u] *Departamento de Dermatología, Hospital Universitario Dr. Peset, Valencia, Spain*
[v] *Departamento de Dermatología, Hospital Universitario Son Llàtzer, Palma, Islas Baleares, Spain*
[w] *Departamento de Dermatología, Hospital Universitario Nuestra Señora De Valme, Sevilla, Spain*
[x] *Departamento de Dermatología, Hospital Universitario de Araba, Vitoria-Gasteiz, Álava, Spain*
[y] *Departamento de Dermatología, Hospital Universitario de Salamanca, Salamanca, Spain*
[z] *Departamento de Dermatología, Hospital General de Ciudad Real, Ciudad Real, Spain*
[aa] *Departamento de Dermatología, Hospital Germans Trias i Pujol, Barcelona, Spain*
[ab] *Departamento de Dermatología, Hospital Universitario del Henares, Coslada, Madrid, Spain*
[ac] *Departamento de Dermatología, Hospital Universitario de Torrejón, Torrejón de Ardoz, Madrid, Spain*
[ad] *Departamento de Dermatología, Complejo Asistencial Universitario de León, León, Spain*
[ae] *Departamento de Dermatología, Hospital Puerta del Mar, Cádiz, Spain*
[af] *Unidad de Investigación, Fundación Piel Sana AEDV, León, Spain*
[ag] *Departamento de Dermatología, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain*

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Abstract:
Background and objective: Primary cutaneous lymphomas (PCL) are uncommon. Observations based on the first year of data from the Spanish Registry of Primary Cutaneous Lymphomas (RELCP, in its Spanish abbreviation) of the Spanish Academy of Dermatology and Venereology (AEDV) were published in February 2018. This report covers RELCP data for the first 5 years.
Patients and methods: RELCP data were collected prospectively and included diagnosis, treatments, tests, and the current status of patients. We compiled descriptive statistics of the data registered during the first 5 years.
Results: Information on 2020 patients treated at 33 Spanish hospitals had been included in the RELCP by December 2021. Fifty-nine percent of the patients were men; the mean age was 62.2 years. The lymphomas were grouped into 4 large diagnostic categories: mycosis fungoides/Sézary syndrome, 1112 patients (55%); primary B-cell cutaneous lymphoma, 547 patients (27.1%); primary CD30^{+} lymphoproliferative disorders, 222 patients (11%), and other T-cell lymphomas, 116 patients (5.8%). Nearly 75% of the tumors were registered in stage I. After treatment, 43.5% achieved complete remission and 27% were stable at the time of writing. Treatments prescribed were topical corticosteroids (1369 [67.8%]), phototherapy (890 patients [44.1%]), surgery (412 patients [20.4%]), and radiotherapy (384 patients [19%]).
Conclusion: The characteristics of cutaneous lymphomas in Spain are similar to those reported for other series. The large size of the RELCP registry at 5 years has allowed us to give more precise descriptive statistics than in the first year. This registry facilitates the clinical research of the AEDV's lymphoma interest group, which has already published articles based on the RELCP data.

PALABRAS CLAVE
Linfomas cutáneos;
Micosis fungoide;
Registros;
Registro español de linfomas de la AEDV

Registro de linfomas cutáneos primarios (RELCP) de la AEDV: datos tras 5 años de funcionamiento

Resumen
Antecedentes y objetivos: Los linfomas cutáneos primarios (LCP) son un conjunto de entidades poco frecuentes. En febrero del 2018 se describieron los resultados del primer año de funcionamiento del Registro de linfomas cutáneos primarios de la AEDV. En el presente trabajo actualizamos los resultados tras 5 años de funcionamiento.
Pacientes y métodos: Registro de enfermedad de pacientes con LCP. Se recogieron datos prospectivamente de los pacientes, incluyendo diagnóstico, tratamientos, pruebas realizadas y estado actual del paciente. Se realizó un análisis descriptivo.
Resultados: En diciembre del 2021 se había incluido a un total de 2.020 pacientes en el Registro, pertenecientes a 33 hospitales españoles. El 59% fueron hombres, y la edad media fue de 62,2 años. Se agruparon en 4 grandes grupos diagnósticos: micosis fungoide/síndrome de Sézary (1.112 [55%]), LCP de células B (547 [27,1%]), trastornos linfoproliferativos de células T CD30+ (222 [11%]) y otros linfomas T (116 [5,8%]). La mayoría presentó estadio T1, encontrándose

actualmente casi el 75% en remisión completa (43,5%) o enfermedad estable (EE: 27%). Los tratamientos más usados fueron corticoides tópicos (1.369 [67,8%]), fototerapia (890 [44,1%]), cirugía (412 [20,4%]) y radioterapia (384 [19%]).
Conclusión. — Las características del paciente con LCP en España no difieren de otras series. El mayor tamaño del registro permite precisar mejor los datos con respecto a los resultados del primer año. Este registro facilita al grupo de linfomas de la AEDV realizar investigación clínica, surgiendo ya trabajos publicados de dicho registro.

Introduction

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of entities characterized by the primary proliferation of different types of lymphocytes (T cells, B cells, and natural killer cells) in the skin, from where they can spread to the peripheral blood, lymph nodes, and even other organs. They may follow a progressive course and can affect quality of life and have serious consequences.[1]

Clinical registries are a very useful tool for uncommon, frequently difficult-to-manage, entities, such as PCL. In December 2016, the Spanish Academy of Dermatology and Venereology (AEDV) started a multicenter registry (RELCP, in its Spanish abbreviation) to collect clinical data on PCL.[2] The report summarizing the data collected in the first year of the registry was published in February 2018.[3] The aim of this study was to summarize observations for the first 5 years of the registry, with a focus on the clinical characteristics of the patients seen at the participating hospitals and the treatments used.

Material and Methods

The AEDV's RELCP is a prospective multicenter registry to which any hospital with a dedicated or specialized cutaneous lymphoma unit can contribute. All the patients included in the first 5 years of the registry were diagnosed according to the criteria proposed by the World Health Organization and the European Organization for Research and Treatment of Cancer (WHO-EORTC).[1] The participating hospitals included all patients with a diagnosis of PCL seen at their hospital. The only exclusion criterion was patient refusal to participate in the study. Data were entered into an online system provided by the Research Unit of the AEDV Foundation (OpenClinica Open Source software, version 3.1) following a standard protocol. Statistical analyses were performed in Stata (version 17 Statacorp). The study was classified by the Spanish Agency of Medicines and Medical Devices as a non-postauthorization study and approved by the ethics committee at Hospital 12 de Octubre (16/175) and by all participating hospitals. It complied with the principles of the Declaration of Helsinki and current legislation. All patients included in the registry provided written informed consent.

The RECLP includes information collected at inclusion and follow-up visits. At the inclusion visit, a note was made of the following demographic and diagnostic data: date; type of lymphoma according to the WHO classification; stage according to the revised classification system for TNM (or TNMB in the case of mycosis fungoides/Sézary syndrome [MF/SS]) proposed by the International Society for Cutaneous Lymphomas and the Cutaneous Task Force of the EORTC[4–6]; and diagnostic tests and treatments. The information recorded at the follow-up visits included date of last visit; disease status classified as complete remission (100% clearance since last visit), partial remission (50%–99% clearance since last visit), stable disease (< 25% to < 50% clearance since last visit), disease progression (≥ 25% progression since last visit), death, or recurrence; and presence of cutaneous, lymph node, visceral organ, or blood involvement at the time of the visit.

For the purpose of this study, lymphomas were separated into 4 large categories: MF/SS; primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders (CD30$^+$ LPDs), which included lymphomatoid papulosis [LyP] and anaplastic large cell lymphoma [ALCL]); other T-cell lymphomas (TCLs); and B-cell lymphomas (BCLs). The results are reported using absolute numbers and percentages for qualitative variables, mean (SD) for normally distributed continuous variables, and median (range) for nonnormally distributed continuous variables.

Results

At the time of the analysis, December 2021, the registry included data on 2020 patients from 33 Spanish hospitals. There were 830 women and 1190 men with a mean (SD) age of 62.2 (15.6) years and a mean age at inclusion of 55.7 (15.9) years. Age at disease onset ranged from 10 to 97 years. The mean duration of disease was 5.1 (5.8) years. The numbers of patients added annually to the registry over the first 5 years are shown in Fig. 1.

Diagnostic Categories

There were 1112 patients (55% of all patients) in the MF/SS category, 222 (11%) in the CD30$^+$ LPD category, 116 (5.8%) in the other TCL category, and 574 (27.1%) in the BCL category. The remaining 23 patients (1.2%) were not classified. The full breakdown by type of lymphoma is shown in Table 1.

The most common diagnoses in the MF/SS category were classic MF (882, 79.3% of patients in this category and 43.7% of all patients); 171 patients had folliculotropic MF and 55

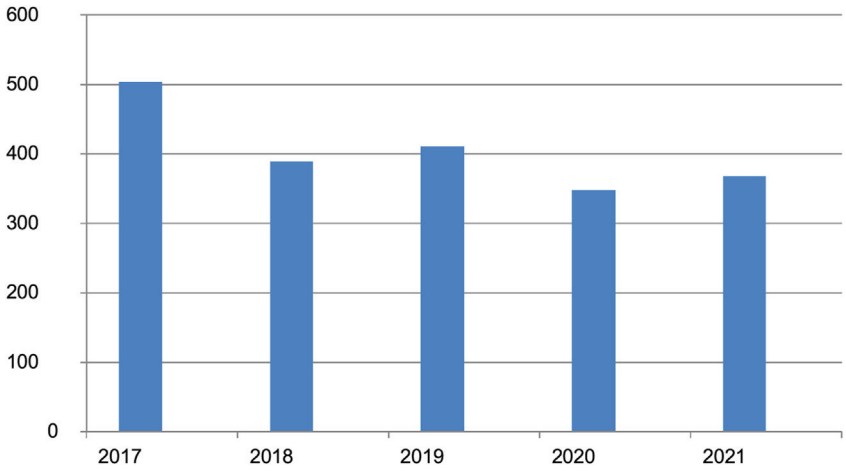

Figure 1 Number of patients added annually to the list during the first 5 years of the Spanish Primary Cutaneous Lymphoma Registry.

Table 1 Total Number (%) of Lymphomas Included in the Spanish Primary Cutaneous Lymphoma Registry According to Eortc Diagnostic Criteria, Ordered by Frequency.

EORTC diagnosis	No.	%
Mycosis fungoides without further specification	882	43.7
Marginal zone B-cell lymphoma	280	13.9
Follicle-center B-cell lymphoma	229	11.3
Folliculotropic mycosis fungoides	171	8.5
Lymphomatoid papulosis	152	7.5
$CD4^+$ small/medium T-cell lymphoproliferative disorder	76	3.8
Anaplastic large-cell lymphoma	70	3.5
Sézary syndrome	56	2.8
Diffuse large B-cell lymphoma, leg type	31	1.5
Other lymphomas	22	1.1
Nonspecified peripheral T-cell lymphoma	20	1.0
Subcutaneous panniculitis-like T-cell lymphoma	7	0.3
Gamma-delta T-cell lymphoma	3	0.1
Acral $CD8^+$ T-cell lymphoma	3	0.1
Pagetoid reticulosis	2	0.1
$CD8^+$ epidermotropic cytotoxic T-cell lymphoma	2	0.1
Extranodal nasal-type natural killer/T-cell lymphoma	2	0.1
Intravascular B-cell lymphoma	2	0.1
EBV^+ diffuse large B-cell lymphoma	2	0.1
Granulomatous slack skin	1	0.0
Follicular T-cell lymphoma	1	0.0
Hydroa vacciniforme-like lymphoproliferative disease	1	0.0
EBV^+ mucocutaneous ulcer	1	0.0
Angioimmunoblastic T-cell lymphoma	1	0.0
Plasmacytoid dendritic cell neoplasm	1	0.0
Hodgkin lymphoma	1	0.0
Posttransplant lymphoproliferative disorder	1	0.0
Total	2020	100

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; EBV, Epstein–Barr virus.

had SS (15.3% and 5% of all patients in the MF/SS category, respectively).

BCLs were the second largest category. The most common diagnoses were marginal zone B-cell lymphoma (MZL) and follicle-center B-cell lymphoma (FCL), with 280 (51.2%) and 229 (41.9%) cases, respectively.

In the $CD30^+$ LPD category, lymphomatoid papulosis accounted for approximately twice as many cases as $CD30^+$ anaplastic large cell lymphoma (152 [68.5%] vs 70 [31.5%]).

The smallest category was other TCLs, the most common of which was $CD4^+$ small/medium T-cell lymphoproliferative disorder (76, 65.5% of all cases in this category).

Table 2 TNM Stages (TNMB Stages for MF/SS) (% of Total Sample).

	MF/SS			Non-MF/SS lymphomas		
	Stage	No.	%	Stage	No.	%
T stage (skin)	**T1**	110	9.9	**T1**	125	13.8
	T1a	286	25.7	T1a	318	35
	T1b	172	15.5	T1b	54	5.9
	T2	95	8.5	T2	27	3
	T2a	98	8.8	T2a	92	10.1
	T2b	128	11.5	T2b	43	4.7
	T3	98	8.8	T2c	17	1.9
	T4	89	8	T3	36	4.0
	Unknown	36	3.2	T3a	49	5.4
				T3b	90	9.9
				T4	3	0.3
				Unknown	54	5.9
N stage (lymph nodes)	N0	988	88.8	N0	823	90.6
	N1	44	3	N1	20	2.2
	N2	3	1.3	N2	6	0.7
	N3	6	0.5	N3	4	0.4
	Nx	25	2.2	Nx	2	0.2
	Unknown	46	4.1	**Unknown**	59	6.5
M stage (organs)	M0	1062	95.5	M0	844	93
	M1	2	0.2	M1	4	0.4
	Unknown	48	4.3	**Unknown**	60	6.6
B stage (peripheral blood)* MF/SS	B0	970	87.2			
	B1	32	2.9			
	B2	43	3.9			
	Unknown	67	6			

Abbreviation: MF/SS, mycosis fungoides/Sézary syndrome.

Stages

TNM/TNMB stages for the full sample are shown in Table 2. In terms of cutaneous involvement, 1065 patients (52.7%) had stage T1 disease at diagnosis, and of these 604 (29.9% of all patients) were stage T1a. Five-hundred patients had stage T2 disease (24.8%), 273 (13.5%) T3 disease, and 92 (4.6%) T4 disease. The degree of cutaneous involvement in the remaining 90 cases was recorded as unknown or not applicable.

The immense majority of patients (1811, 89.7%) did not have lymph node involvement at the time of this study. In 132 patients (6.5%), lymph node status was recorded as unknown, not evaluated, or not applicable. Just 77 patients (3.8%) had lymph node involvement. Visceral organ involvement at diagnosis was very uncommon (6 patients, 0.3%).

The breakdown and distribution of disease stages according to a diagnosis of MF/SS vs. a non-MF/SS lymphoma are shown in Table 2. Just 6.8% of patients with MF/SS had peripheral blood involvement.

Overall clinical stages for patients with MF/SS are shown in Table 3. Almost three-quarters of the patients (826/1112, 74.3%) had stage I disease, and within this category, the majority (518, 46.6%) were stage IA; 184 patients (16.6%) had advanced disease (stage IIB or higher). Stage was unknown for 6.3% of patients.

Table 3 Clinical Stage in Mycosis Fungoides/Sézary Syndrome Group at Inclusion in the Spanish Primary Cutaneous Lymphoma Registry.

Clinical stage	No.	%
IA	518	46.6
IB	308	27.7
IIA	32	2.9
IIB	92	8.3
IIIA	18	1.6
IIIB	17	1.5
IVA1	45	3.7
IVA2	9	0.8
IVB	3	0.3
Unknown	70	6.3
Total	1112	100

Diagnostic Procedures

Histologic examination was performed in all patients, and laboratory tests in the vast majority (1980/2020, 98%). Immunohistochemical studies were performed in 1909 patients (94.5%) and molecular studies in 1358 (67.2%).

Imaging studies were performed in 1491 patients (73.8%), and additional radiological tests in 1677 (83%).

Table 4 Breakdown of Treatments Reported in the Spanish Primary Cutaneous Lymphoma Registry.

Treatment	No.	%
Topical corticosteroids	1369	67.8
Topical nitrogen mustard	23	1.1
Topical carmustine (BCNU)	24	1.2
Topical bexarotene	31	1.5
PUVA	484	24.0
Re-PUVA	34	1.7
Narrow-band UV-B	372	18.4
Electron beam therapy	66	3.3
Radiotherapy	384	19.0
Systemic chemotherapy	246	12.2
Surgery	412	20.4
Systemic retinoids	92	4.6
Interferon	163	8.1
Fusion antibodies with toxins	6	0.3
Histone deacetylase inhibitors	11	0.5
Intravenous anti-CD20 antibodies	107	5.3
Subcutaneous anti-CD20 antibodies	71	3.5
Bone marrow transplant	25	1.2

Abbreviations: PUVA, psoralen plus UV-A therapy; Re-PUVA, PUVA combined with retinoids.

Treatments

The treatments used to manage PCL are shown in Table 4. Topical corticosteroids were by far the most widely prescribed treatment (1369 patients, 67.8% of total). These were followed by different forms of phototherapy (890 patients, 44.1%), surgery (412, 20.4%), and radiotherapy (384, 19%).

Approximately two-thirds of patients received 1 (713, 35.3%) or 2 (623, 30.9%) treatments; 327 (16.2%) received 3 treatments and 316 (15.7%) 4 or more. Just 41 patients (2.0%) did not receive any treatment for the management of their PCL.

Clinical Course

Treatment responses and disease status are shown in Tables 5 and 6. Just over half of the patients (1134, 56.1%) responded to treatment, with most achieving a complete response. Stable disease was recorded for 546 patients (27%) at the time of this study. Approximately 10% had progressive disease or had died.

At the time of our analysis, 962 patients (47.6%) had cutaneous involvement versus 950 (47.0%) who did not. No data were available for the remaining 5.4% of patients. The respective figures for lymph node, visceral organ, and peripheral blood involvement were 4.2% (84), 1.2% (24), and 3.6% (72).

Comparisons between patients with MF/SS and non-MF/SS lymphomas are also shown in Tables 5 and 6. The main difference observed was for the percentage of patients who had achieved complete remission, which is reflected in the percentage of those with cutaneous involvement at the time of the study: more than 60% of non-MF/SS patients had achieved a complete response compared with less than 30% of MF/SS patients. In addition, disease progression was almost twice as common in the MF/SS category (7% vs. 3.5%).

Discussion

PCLs are rare, with an estimated annual incidence of approximately 1 case per 100 000 people.[7] Several studies in Germany,[8] the United Kingdom,[9] Norway,[10] Denmark,[11] and France[12] have reported incidence rates of between 2.9 and 4 cases $\times 10^6$ a year. The creation of a national PCL registry 5 years ago was prompted by the low incidence of these diseases. It was designed to facilitate collaborative research and has already led to several publications in international journals over the years.[13–15] In addition, the number of patients added to the registry each year has remained stable, within a range of between 348 and 411 patients, following the initial 504 included in year 1. (The higher initial number is to be expected as hospitals will have included nonincident cases.) The similarity between the numbers in the first and following years can largely explained by the notable increase in the number of hospitals contributing to the registry, which has risen from 16 in year 1 to the current number of 33.

The breakdown of diagnoses is similar to that described in the literature,[1,16] albeit with slight differences. T-cell lymphomas accounted for 72% of diagnoses, compared with 27% for BCLs. MF together with its variants was the most common entity (52.3%), followed by MZL (13.9%) and FCL (11.3%).

Table 5 Treatment Responses in MF/SS and non-MF/SS Groups.

Patient status at time of study	MF/SS		Non-MF/SS		Total	
	No.	%	No.	%	No.	%
Complete remission	307	27.6	574	63.2	881	43.6
Partial remission	197	17.7	59	6.5	256	12.7
Stable disease	413	37.1	133	14.6	546	27.0
Progressive disease	78	7.0	32	3.5	110	5.4
Loss to follow-up	54	4.9	63	6.9	117	5.8
Deceased	55	4.9	31	3.4	86	4.3
Relapse	7	0.6	15	1.7	22	1.1
Unknown	1	0.1	1	0.1	2	0.1

Abbreviation: MF/SS, mycosis fungoides/Sézary syndrome.

Table 6 Disease Course by Compartment in MF/SS and non-MF/SS Groups.

Current status	MF/SS		Non-MF/SS (rest)		Total	
	No.	%	No.	%	No.	%
Cutaneous disease at time of study						
No	344	30.9	622	68.5	966	47.8
Yes	711	63.9	238	26.2	949	47.0
Unknown	57	5.1	48	5.3	105	5.2
Lymph node involvement at time of study						
No	937	84.3	810	89.2	1747	86.5
Yes	64	5.8	20	2.2	84	4.2
Unknown	111	10.0	78	8.6	189	9.4
Visceral organ involvement at time of study						
No	962	86.5	802	88.3	1764	87.3
Yes	16	1.4	8	0.9	24	1.2
Unknown	134	12.1	98	10.8	232	11.5
Blood involvement at time of study						
No	896	80.6	713	79.0	1609	79.9
Yes	64	5.8	8	0.9	72	3.6
Unknown	152	13.7	182	20.2	334	16.6

Abbreviation: MF/SS, mycosis fungoides/Sézary syndrome.

Contrasting with reports in the latest update of the WHO-EORTC classification for PCLs,[1] we observed a slightly higher proportion of MF and BCL cases. Mean age at diagnosis was 55.6 years, and the ratio of male to female patients was 1.4:1. These findings are similar to those reported for the first year of the registry.[3] The proportions of MZL and FCL in the BCL category and LyP and ALCL in the CD30$^+$ LPD category are also very similar to those in the first year.[3] Of note in year 1 and now is the practically identical number of MZL and FCL cases. This similarity was not reflected in the latest large-scale revisions,[1,16] although it has been described in other studies.[8] The profile of CD30$^+$ LPDs is also similar to that described in the literature.[1,17,18] LyP, with twice as many cases as ALCL and CD4$^+$ small/medium T-cell LPDs, remains the second most common T-cell LPD (10.5% of cases in this category, 7.5% of total).

Advanced disease accounted for just a small proportion of cases in the RELCP; 16.5% of patients with MF/SS had stage IIB disease or higher, and just 8.2% of these were stage III-IV. Advanced disease was also uncommon in the other categories. Observations from the RELCP registry suggest that MF/SS follows a worse disease course, as patients in this group were almost twice as likely to develop progressive disease as those with a non-MF/SS lymphoma, and these in addition were twice as likely to achieve complete remission.

The RECLP registry has some limitations, including the potential inaccuracy of some diagnoses (procedures are not centralized) and variability between hospitals. Even though clinical guidelines help standardize procedures and treatments, there will be inevitable differences such as greater or lesser access to diagnostic resources, such as genetic tests. The proportion of patients seen by the dermatology department may also vary, as in some hospitals, patients with more advanced disease or severe manifestations will be under the care of the hematology department. Nevertheless, the large number of hospitals that contribute to the registry and the consecutive enrolment of patients by all hospitals should limit the risk of selection bias and ensure a true reflection of PCL in Spain.

Conclusions

Overall, the clinical characteristics of patients with PCL in Spain are similar to those described in other series. The classic breakdown of 75% vs. 25% for MF/SS vs. non-MF/SS lymphomas was maintained. MF was by far the most common entity, followed by MZL and FCL. At the time of this study, most patients had early-stage disease, more than 50% had responded completely or partly to treatment, and 25% had stable disease.

The AEDV's PCL registry facilitates clinical studies on this rare group of diseases and provides easy access to groups of patients for subsequent studies, including those with a prospective design.

Conflicts of Interest

The Spanish Registry of Primary Cutaneous Lymphomas (RELCP) is sponsored by the Healthy Skin Foundation of the Spanish Academy of Dermatology and Venereology. Kyowa Kirin helps with funding to maintain the registry. Collaborating companies have no role in the design or conduct of studies, the writing of manuscripts, or publication decisions.

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