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ORIGINAL ARTICLE

Distribution of lymphomas in Mexico: a multicenter descriptive study

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Abstract

Epidemiology of lymphoma is not well described in Mexico. We determined the frequencies and subtypes of the main non-Hodgkin's and Hodgkin's lymphomas in the Mexican population. Files for tissue samples for lymphomas stored in five different hospitals in Mexico City were retrieved for re-analysis and further immunostaining. The most common mature B cell, T cell/NK cell, Hodgkin's, and precursor lymphoid neoplasms were identified according to the 2008 WHO classification of tumors. All stains were performed in the same laboratory and interpreted by three pathologists. Five thousand seven hundred seventy-two neoplasms were included. Of these, 4213 were mature B cell neoplasms (73%; 95% CI 71.83–74.12), 888 Hodgkin's lymphomas (HLs) (15%; 95% CI 14.48–16.34), 496 mature T cell/NK neoplasms (9%; 95% CI 7.89–9.34), and 175 precursor lymphoid neoplasms (3%; 95% CI 2.62–3.5). Neoplasms had an even distribution between sexes. Main mature B cell lymphomas were diffuse large B cell lymphoma (DLBCL) (56%; 95% CI 54.39–57.39) and follicular lymphoma (FL) (20%; 95% CI 18.92–21.34). Hodgkin's lymphomas were also classified into five main subtypes, with nodular sclerosis (47%; 95% CI 44.14–50.7) and mixed cellularity (38%; 95% CI 34.49–40.85) being the most common. The most common mature T cell/NK neoplasm was peripheral T cell lymphoma NOS/anaplastic large cell lymphoma ALK negative (44%; 95% CI 39.85–48.84). This is the first descriptive study in Mexico with a large sample of lymphomas classified according to the 2008 WHO classification. The results obtained are in keeping with the numbers described in other populations.

Keywords Hodgkin's lymphoma · Non-Hodgkin's lymphoma · T cell

Background

Cancer is the second leading cause of death in the USA and one of the three most common causes in higher income countries. Lymphomas, including both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), are the sixth most common neoplasms in the USA, constituting 4.8% of all new cancers each year and 3.5% of yearly cancer deaths [1, 2].

Adrian Carballo-Zarate and Alejandro Garcia-Horton contributed equally to this work.

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Mexico is in epidemiologic transition, meaning that chronic-degenerative diseases and cancer are increasingly gaining importance with decreasing mortality of infectious diseases [3]. The recorded mortality rate in Mexico due to neoplastic diseases more than doubled between the years of 1955 and 2002, increasing from 28.1 to 57.2 cases per 100,000 individuals [4]. As of 2013, cancer became the third leading cause of death in Mexico [5].

In Latin America, NHLs are listed by the WHO as the eighth most common malignancy [6]. In Mexico, the latest registry of malignant neoplasms was completed in 2002. It listed lymphoma and leukemia among the 15th most frequent neoplasms constituting 8.2% of the total cancers. Unfortunately, accurate and up to date registries are lacking and an effort to improve this area of epidemiology in Mexico is important [4].

The World Health Organization (WHO) updated in 2017 the classification system for hematopoietic and lymphoid tissue tumors. The previous classification and fourth edition were published in 2008 and both serve as worldwide guidelines and consensus definitions to the different hematological malignancies. These are based on the revised European-American classification of lymphoid neoplasms (REAL) proposed by the International Lymphoma Study Group (ILSG) [7, 8]. They are relevant to provide context and appropriate organization for epidemiologic, management, and future research. The 2008 and the updated 2017 WHO classifications consider each type of lymphoma as a unique entity which is defined by its morphology, immunophenotype, clinical findings, and cytogenetic abnormalities. Pathologists are advised to use this system in daily practice and be aware that the lymphoid neoplasms must be analyzed based not only on morphology but also on immunophenotype at a minimum, to reach an accurate diagnosis.

The epidemiology and distribution of lymphoma subtypes are well known in higher income countries [1, 9, 10]; however, in Mexico, the data is limited and dated and has several methodological limitations [11–15]. Thus, this study aimed to provide updated information about the epidemiology of lymphomas in Mexico from five high-volume referral centers, and report on their morphology and immunophenotype based on the 2008 WHO classification of lymphoid tissues.

Methods

Files from the period between January 1, 2005, and December 31, 2014, for consecutive tissue samples with a diagnosis of lymphoma that were stored in five different hospitals in Mexico City (Hospital Español de México, Hospital Ángeles del Pedregal, Hospital Ángeles de las Lomas, Centro Médico Nacional La Raza, and Laboratorio de Patología, Inmunohistoquímica y Citopatología, SC (PIC)) were retrieved for re-analysis. Excel (Microsoft, Redmond, WA) was used for the documentation of demographic data (i.e., age and sex) as well as for statistical analysis.

All the cases that had tissue sections available from storage in paraffin blocks were cut at a width of 2 to 3 μm and were stained with hematoxylin and eosin. The biopsies were processed according to local protocols in the participating laboratories and were fixed in 10% formalin buffer for 6 to 48 h. Specific immunostaining (Table 1) was performed for the different diagnostic possibilities including diffuse large B cell lymphomas (DLBCL), small B cell lymphomas (SBCL), B cell lymphomas with plasmacytoid differentiation, Hodgkin's lymphomas, and mature T/NK cell lymphomas. Immunostaining for all cases was completed in one laboratory (PIC) and interpreted by the same three pathologists. Diagnoses of precursor B cell lymphomas were excluded from further characterization. Hematopoietic neoplasia with null immunophenotype and plasma cell neoplasms were excluded from our analysis. Lymphomas were classified based on the morphological and immunophenotypic criteria specified by the 2008 WHO criteria [8] as provided by the three participating pathologists. Data is presented using simple proportions and 95% confidence intervals were calculated using the Wilson score method [16].

Results

We included 5772 lymphoid neoplasms from January 1, 2005, to December 31, 2014, in this study. Of these, 4213 were classified as mature B cell neoplasms (73%; 95% CI 71.83–74.12), 888 as Hodgkin's lymphomas (15%; 95% CI 14.48–16.34), 496 as mature T cell/NK neoplasms (9%; 95% CI 7.89–9.34), and 175 as precursor lymphoid neoplasms (3%; 95% CI 2.62–3.5) (Table 2). An even distribution between sexes was observed throughout the different neoplasms, with 51% of the cases being male patients. Figure 1 summarizes the distribution of lymphoma cases in Mexico.

All four different categories of neoplasms were further analyzed and classified according to the 2008 WHO classification as specified in the "Methods" section. Six mature B cell lymphomas accounted for almost 95% of all B cell neoplasms. These included diffuse large B cell lymphoma (DLBCL) (56%; 95% CI 54.39–57.39), follicular lymphoma (FL) (20%; 95% CI 18.92–21.34), mantle cell lymphoma (6.7%; 95% CI 6.02–7.53), marginal zone/MALT lymphoma (5.2%; 95% CI 4.59–5.93), chronic lymphocytic leukemia/small lymphocytic lymphoma (4.6%; 95% CI 4.01–5.28), and Burkitt's lymphoma (2.5%; 95% CI 2.04–2.98) (Table 2). Other B cell neoplasms accounting for almost 5% of the cohort were identified but consisted individually in less than 1.4% of the total cases. These included hairy cell leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic B cell

Table 1 Specific immunostaining performed on tissue samples for distinct lymphomas

DLBCL	CD20, CD3, bcl-6, CD10, bcl-2, Ki-67
SBCL	CD20, CD5, CD23, cyclin D1, bcl-6, CD10, Ki-67
BCLs with plasmacytoid differentiation	CD79a, PAX-5, CD138, kappa/lambda restriction, EBER (if applicable)
Hodgkin's lymphomas	CD20, CD3, CD45, CD30, CD15, LMP-1
Mature T/NK cell lymphomas	CD20, CD3, CD43, Ki-67, CD4, CD8, CD30, CD56, ALK-1, EMA, Ki-67, TIA-1, Perforin, Granzyme B, EBER (if applicable)

DLBCL, diffuse large B cell lymphoma; *SBCL,* small B cell lymphoma; *BCLs*, B cell lymphomas; *EBER*, Epstein-Barr virus in situ hybridization

lymphoma, and unclassifiable B cell lymphoma with features intermediate between DLBCL and classical Hodgkin's lymphoma.

Hodgkin's lymphomas were also classified into the five main subtypes, with nodular sclerosis (47%; 95% CI 44.14–50.7) and mixed cellularity (38%; 95% CI 34.49–40.85) being the most common and accounting for 85% of all HL cases (Table 2). Lymphocyte depleted, lymphocyte rich, nodular lymphocyte predominant, and unclassifiable classical HL contributed each with less than 7% of the cases.

Table 2 Distribution of lymphoid neoplasms

Neoplasm type	Number of cases	Percentage	95% CI
All lymphoid neoplasms			
Mature B cell neoplasms	4213	73	71.83–74.12
Mature T cell/NK neoplasms	496	9	7.89–9.34
Precursor lymphoid neoplasms	175	3	2.62–3.5
Hodgkin's lymphomas	888	15	14.48–16.34
Total neoplasms	5772	100	
Mature B cell neoplasms			
Diffuse large B cell lymphoma	2355	55.90	54.39–57.39
Follicular lymphoma	847	20.10	18.92–21.34
Mantle cell lymphoma	284	6.74	6.02–7.53
Nodal marginal zone or extranodal (MALT) lymphoma	220	5.22	4.59–5.93
Chronic lymphocytic leukemia/small lymphocytic lymphoma	194	4.60	4.01–5.28
Burkitt's lymphoma	104	2.47	2.04–2.98
Others	209	4.96	4.34–5.65
Total	4213	100	
Mature T cell/NK neoplasms			
Peripheral T cell lymphoma NOS/anaplastic large cell lymphoma ALK -	206	44.3	39.85–48.84
Extranodal NK/T cell lymphoma, nasal type	137	29.5	25.5–33.76
Anaplastic large cell lymphoma ALK+	59	12.7	9.96–16.02
Mycosis fungoides	23	4.9	3.32–7.31
Angioimmunoblastic T cell lymphoma	15	3.2	1.96–5.25
Others	25	5.4	3.67–7.82
Total	465	100	
Hodgkin's lymphoma			
Nodular sclerosis	421	47	44.14–50.7
Mixed cellularity	334	38	34.49–40.85
Lymphocyte depleted	58	7	5.08–8.35
Nodular lymphocyte predominant	32	4	2.56–5.04
Lymphocyte rich	25	3	1.91–4.12
Classical unclassifiable	18	2	1.28–3.18
Total	888	100	

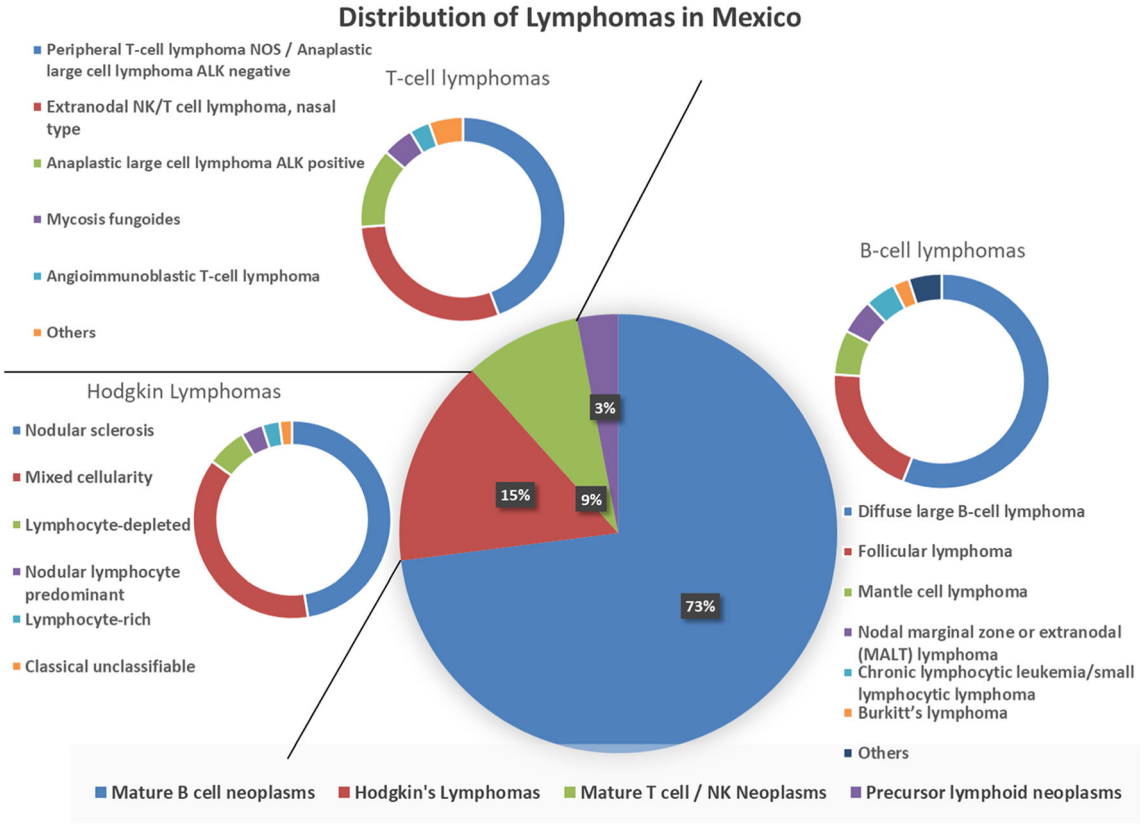

Fig. 1 Summary of distribution of lymphomas in Mexico

Several mature T cells/NK neoplasms were identified, with the majority of cases being peripheral T cell lymphoma NOS/ anaplastic large cell lymphoma ALK negative (44%; 95% CI 39.85–48.84) and extranodal NK/T cell lymphoma, nasal type (30%; 95% CI 25.5–33.76) (Table 2). Other identified lymphomas included ALK-positive anaplastic lymphoma, mycosis fungoides, and angioimmunoblastic T cell lymphoma. Again, about 5% of the total T cell lymphomas were accounted by rare lymphomas presenting with 9 or fewer cases in the cohort and including primary cutaneous gamma-delta T cell lymphoma, primary cutaneous CD8- or CD4-positive T cell lymphoma, and hepatosplenic T cell lymphoma.

Analysis of the cases by group age was also performed for mature B cell neoplasms and HL. Patients were classified into different age categories in intervals of 20 years. Figure 2 shows a graph comparing distribution in age groups for the main B cell neoplasms. The majority of the B cell neoplasms occurred in the age group between 61 and 80 years old, followed by the group between 41 and 60 years old. This applied also to the 2 most common B cell malignancies, DLBCL and follicular lymphoma. Eight hundred sixty-five (36.7%) cases of DLBCL were identified in the group between 61 and 80 years old and 660 (28%) in the 41–60 years old group. For follicular lymphoma, 309 (36.5%) cases were in the 41–60 years old age group and 274 (32.3%) in the 61–80 years old group. Burkitt's lymphoma occurred evenly throughout age groups 2–20, 21–40, and 41–60 years old with an average of 25 cases per group.

In the case of HL, the majority of nodular sclerosis subtypes were seen in the group age of 21–40 years old with 175 (41.6%) cases. Eighty-one (19.2%) cases were observed in the 2–20 years old group, although the majority was closer to 19 years of age. Sixty-one (14.5%) cases occurred in the 41–60 age group, with most of the cases presenting in the late 50's. Mixed cellularity subtype showed a more even distribution in the age groups between 21 and 80 years old. Eighty-

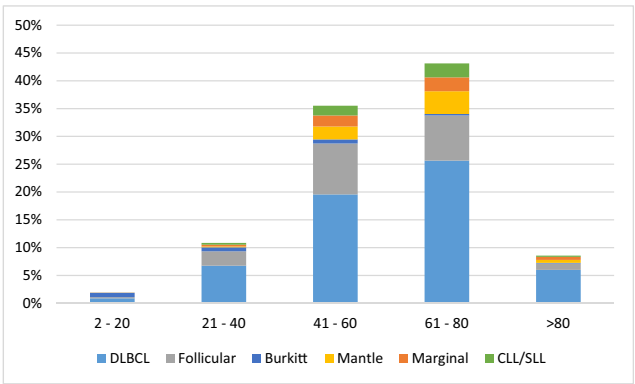

Fig. 2 Age distribution in mature B cell neoplasms. A total of 631 cases were excluded from this figure since age was not provided in the identification data

seven (26%) cases were identified in the 21–40 years old age group. The rest of HL subtypes also had an even distribution between age groups. Figure 3 shows more details related to age distribution in HL.

Discussion

The incidence of lymphoma continues to increase in Mexico, with various factors playing a role on it including improvements in detection systems, increase in the population's life expectancy, chronic viral and bacterial infections, exposure to chemical products as benzene, polycyclic aromatic hydrocarbons, pesticides, and ionizing radiation [17, 18], genetic factors, and probably ethnicity [19]. However, no accurate data exist in the distribution of the different lymphoma types. This is the first descriptive study with a large sample of confirmed lymphoid neoplasms, using a standardized method of staining, classified according to the 2008 WHO classification of tumors representative of the Mexican population. It serves as a complement to the current epidemiologic registry of neoplasms in Mexico, adding classification details according to global standards set by the WHO. Our study showed a distribution of about 85% NHLs and 15% HLs. Eighty-six percent of the NHLs corresponded to B cell neoplasms, with the rest being T cell lymphomas. This is consistent with similar series published for Latin America [20] and the world [21, 22].

Unfortunately, until today, a complete histopathologic record of lymphoid malignancies with accurate classification according to WHO criteria does not exist in Mexico [23]. In the present study, we observed consistency and certain differences throughout our results with the prevalence of lymphomas reported in other areas of the world. For example, all grades of follicular lymphoma comprised 20.1% of our B cell lymphomas, comparable with values reported for Central and South America but lower than the 33.8% for North America [20] and higher than the 15.9% for Western Europe [17]. DLBCL accounted for 55.9% of B cell neoplasms in our series, being slightly higher than the average 40% reported for Central and South America and the WHO's 42%, but consistent with Peru's average [20]. A possible explanation of the higher frequencies of DLBCL in Mexico is the late presentation and search of medical attention by some patients due to low education and socioeconomic status. This allows for low-grade lymphomas to progress and transform into aggressive lymphomas without a diagnosis being made prior to the development of significant symptomatology [24–26].

Histopathologic diagnosis of T cell lymphomas is complex and requires a greater number of antibodies as compared to B cell lymphomas [27]. Our series reports T cell lymphomas comprising around 10% of NHLs, again consistent with what has been observed in Central and South America [20]. It is known that T cell neoplasms vary from geographical area to another, with Japan for example reporting them as up to 18% of their NHLs [28, 29]. Most of our cases (44.3%) are peripheral T cell lymphomas NOS. It is possible that this group is overrepresented as some of the subclassifications of T cell neoplasms were unable to be tested for due to economical limitations. As such, some lymphomas were classified as peripheral T cell lymphomas NOS but may have belonged to another category if further testing could have been performed. A high number (29.5%) of extranodal NK/T cell lymphoma nasal type was observed. Extranodal NK/T cell lymphoma nasal type is more common in Asia and is associated with the Epstein-Barr virus (EBV) [30]. In our series, it represents 2.8% of the NHLs, showing a relatively higher incidence than other areas in the world but consistent with reports from other areas of Latin America like Peru and Chile [20, 31].

Hodgkin's lymphoma represented 15% of our series. Nodular sclerosis subtype was the most common comprising 47% of the HL cases and 7.33% of the series. Most of the remaining cases (38%) were of the mixed cellularity subtype. Nodular lymphocyte predominant comprised 4% of our HL cases. This pattern of predominance, where classical HL conforms the majority and nodular lymphocyte predominant conforms only a minority and usually less than 10% of all HL, is

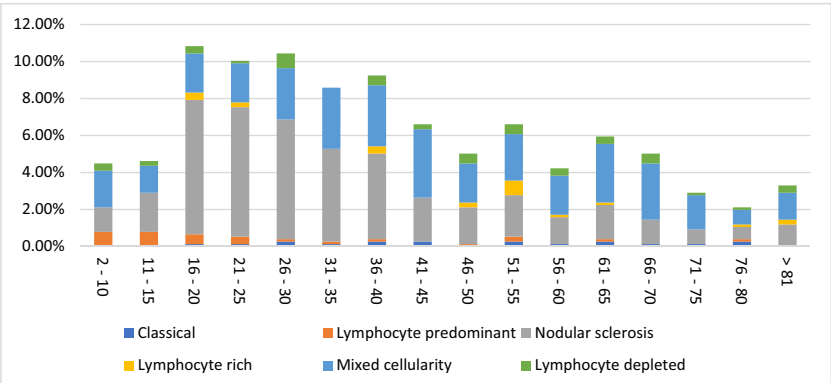

Fig. 3 Age distribution in Hodgkin's lymphoma. A total of 131 cases were excluded from this figure since age was not provided in the identification data

widely observed in the world [7]. The distribution of HL in Mexico followed the usual pattern reported in other series in North America [32–35].

Our study has strengths and limitations. The hospitals involved in providing the data are referral centers for a heterogeneous group of patients from all the Mexican regions. The participating hospitals have distinct population catchment areas, providing a varied socioeconomic and ethnic background to our study. This selection of hospitals provides us with an appropriate cohort of cases required to represent a diverse Mexican population [36]. However, none of the institutions involved in our series are reference centers for pediatric cases, so the population between 2 and 20 years old is most likely underrepresented. Our goal was to provide a distribution of lymphomas mainly in adult population.

To the best of our knowledge, this is the largest series and the first descriptive study of its kind in Mexico studying and analyzing the frequency of lymphoid neoplasms using a consistent and standardized morphological and immunohistochemical approach. The results obtained are in keeping with the numbers described in other population studies worldwide. This study offers an emphasis on the correct classification of these neoplasms based on internationally accepted criteria. It does not intend to replace formal epidemiological records of lymphoid neoplasms in Mexico but it should complement existent epidemiological information.

Authorship AC-Z, AG-H, LP-B, PR-S, RS-V-L, JV-T, and LM-H abstracted the data. AG-H and AC-Z analyzed the data. AZ-O and AL-L conceived the study. AG-H, AC-Z, and AL-L drafted the manuscript. All authors reviewed and approved the final version. All persons who contributed significantly to this work have been acknowledged.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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