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Classification of non-Hodgkin lymphoma in Algeria according to the World Health Organization classification

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Abstract

The relative distribution of non-Hodgkin lymphoma (NHL) subtypes differs markedly around the world. The aim of this study was to report this distribution in Algeria. A panel of four hematopathologists classified 197 consecutive cases according to the World Health Organization classification, including 87.3% B-cell and 12.7% T- or natural killer (NK)-cell NHLs. This series was compared with similar cohorts from Western Europe (WEU) and North America (NA), Algeria had a significantly higher frequency of diffuse large B-cell lymphoma (DLBCL: 52,8%) and a lower frequency of follicular lymphoma (FL: 13.2%) compared with WEU (DLBCL: 32.2%; FL: 20.0%) and NA (DLBCL: 29.3%; FL: 33.6%). The frequency of mantle cell lymphoma was lower in Algeria (2.5%) compared with WEU (8.3%), Smaller differences were also found among the NK/T-cell lymphomas. In conclusion, we found important differences between Algeria and Western countries, and further epidemiologic studies are needed to explain these differences.

Keywords: Non-Hodgkin lymphoma, Algeria, epidemiology, diffuse large B-cell lymphoma

Introduction

The relative distribution of non-Hodgkin lymphoma (NHL) subtypes varies markedly by geographic location around the world [1-5]. However, large and systematic comparative studies are relatively rare in the literature, especially since the World Health Organization (WHO) classification was introduced in 2001 [6]. The WHO classification [6,7] emphasizes the importance of integrating the morphologic,

immunophenotypic, molecular, cytogenetic and clinical findings in order to accurately diagnose lymphomas. However, substantial diagnostic training and technical expertise are needed by the pathologist in order to make a correct diagnosis of lymphoma. Unfortunately, in most countries of the developing world, the diagnostic tools and expertise are limited due to financial constraints.

The International NHL Classification Project was started in 1995 with the goal of investigating the geographic differences in NHL subtype distribution, as well as the clinical features, in various countries around the world [1,8]. During the past 18 years, this group has reviewed cases from 24 countries in six geographic regions of the world using the WHO classification [6]. In April 2012, expert hematopathologists visited Algiers, Algeria, and reviewed cases of lymphoma gathered by the local university hospital and various laboratories and pathology departments in the surrounding region. In this study, we report the distribution of NHL subtypes in Algeria and compare these results with those from North America (NA) and Western Europe (WEU) [1]. To date, a study like this has never been done in Algeria.

Materials and methods

Two hundred and six consecutive, newly diagnosed and untreated cases of NHL were selected for the study. The cases were accrued from 14 February 2009 to 5 September 2011, in the Department of Clinical Hematology (N.B.) of the Pierre and Marie Curie University Hospital in Algiers, Algeria, and various laboratories and pathology departments in the surrounding region (see "Acknowledgements"). The design of this study is similar to our previously published studies

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[1,2,8,9]. Paraffin blocks were sent from Algeria to the Department of Pathology, Hotel-Dieu in Paris (J.A.), where pathology review and staining was performed. As a first step, hematoxylin and eosin (H&E), periodic acid-Schiff, Giemsa and silver impregnation (Gordon-Sweet technique) stains were done on each case. Then, immunohistochemical stains, as well as Epstein-Barr virus encoded small RNA (EBER) in situ hybridization, and molecular studies for immunoglobulin heavy chain and T-cell receptor gamma chain gene rearrangements were performed, as needed, according to the working diagnosis. All submitted cases were initially reviewed by one pathologist (J.A.), who organized the 206 cases for later review by a panel of four experts (J.D., B.N.N., H.K.M.-H. and D.D.W.). All of the case materials, including the slides and results of ancillary studies, were then taken back to Algiers where review by the experts was organized. Clinical data, sometimes limited to age, sex and biopsy site, were available for most cases. Each expert was provided with all of the available material for review including clinical information, stained slides, immunohistochemical stains and results of other ancillary studies that were performed. The four experts each reviewed these materials Independently and recorded their diagnoses using the 2001 WHO classification [6]. A consensus diagnosis was reached In each case when at least three of the four experts agreed. No consensus could be achieved in 21 cases, which were further studied (J.A. and J.D.) with additional immunostains and molecular methods as needed. These cases were then classified according to diagnostic algorithms agreed upon n advance by the four experts, leading to a final consensus diagnosis in all cases [8]. For cases in which a specific

diagnosis was not possible due to suboptimal morphology, loss of antigenicity or inadequate material, the diagnostic categories of unclassifiable low-grade or high-grade B-cell lymphoma were used.

Of the 206 cases, 197 (95.6%) were included in the final analysis and nine (4.4%) were excluded from further analysis. Three of these latter cases were found not to be NHL, including classical Hodgkin lymphoma (n = 1), a diagnosis other than lymphoma (n = 1) and an unclassifiable case (n = 1). As in a previous study [2], we also excluded cases of hairy cell leukemia (n = 2) and chronic lymphocytic leukemia (CLL) diagnosed only by bone marrow examination (n = 4).

Statistical analysis

Data analysis was done using SAS software version 9.3 (SAS Institute Inc., Cary, NC). Comparisons of medians for continuous variables were conducted using the Wilcoxon rank-sum test. Comparisons of categorical variables were done using χ^2 or Fisher's exact tests; the latter was used when the χ^2 test may not have been valid due to small numbers. p-Values for pairwise comparisons were adjusted using the Bonferroni method, and p-values less than 0.05 were considered statistically significant.

Results

The distribution of the NHL subtypes based on the consensus diagnosis is shown in Table I. Of the 197 cases of NHL, 172 (87.3%) were B-cell lymphomas and 25 (12.7%) were T- or natural killer (NK)-cell lymphomas. In five cases

lable I. Frequency of NHL subtypes in Algeria compared with Western Europe and North America.

	Algeria, % (n)	Western Europe, % (n)	North America, % (n)
I-cell lymphomas			
Low-grade	32,5 (64)*†	54.5 (316)	56.1 (224)
Chronic lymphocytic leukemia/small lymphocytic lymphoma	12.2 (24)†	8.6 (50)	4.8 (19)
Follicular lymphoma, all grades	13.2 (26)*†	20.0 (116)	33.6 (134)
Low-grade	3.0 (6)*1	13,3 (77)	22.8 (91)
High-grade	10,2 (20)	6.7 (39)	10.8 (43)
Mantle cell lymphoma	2.5 (5)*	8.3 (48)	7.0 (28)
Marginal zone B-cell lymphoma, MALT type	0.0 (0)*†	10.5 (61)	6.3 (25)
Marginal zone lymphoma, nodal/splenic	2.5 (5)	3.8 (22)	1.8 (7)
Lymphoplasmacytic lymphoma	0.0 (0)	1.4(8)	1.5 (6)
Plasmacytoma	0.0(0)	0.7(4)	0.0 (0)
Unclassifiable low-grade B-cell lymphoma	2.0 (4)	1.2 (7)	1.3 (5)
High-grade	54.8 (108)*f	36.4 (211)	34.3 (137)
Diffuse large B-cell lymphoma	52.8 (104)*†	32.2 (187)	29.3 (117)
High-grade B-cell lymphoma, Burkitt-like	1.0(2)	2.4 (14)	2.5 (10)
Burkitt lymphoma	0.0(0)	0.9 (5)	0.8 (3)
Precursor B-cell lymphoblastic leukemia/lymphoma	0.5(1)	0.2(1)	0.5(2)
Unclassifiable high-grade B-cell lymphoma	0.5 (1)	0.7(4)	1.3 (5)
Subtotal	87.3 (172)	90.9 (527)	90.5 (361)
-cell lymphomas	, ,	• •	
Peripheral T-cell lymphomas	6.1 (12)	7,4 (43)	5.3 (21)
Extranodal NK/T-cell lymphoma, nasal type	3.0 (6)*†	0.5 (3)	0.0 (0)
Precursor T-lymphobiastic leukemia/lymphoma	3.6 (7)*	0.9 (5)	2.0 (8)
Adult T-cell leukemia/lymphoma	0.0 (0)	0.2(1)	0.0(0)
Mycosis fungoides	0.0 (0)	0.2(1)	2.3 (9)
Subtotal	12.7 (25)	9.1 (53)	9.5 (38)
otal	197	580	399

HL, non-Hodgkin lymphoma, NK, natural killer. Significantly different from Western Europe, p < 0.05. ignificantly different from North America, p < 0.05.

of B-cell lymphoma, a specific lymphoma subtype could not be assigned due to suboptimal biopsy material; four (2.0%) were diagnosed as unclassifiable low-grade B-cell lymphoma and one (0.5%) as unclassifiable high-grade B-cell lymphoma. Among the B-cell lymphomas, diffuse large B-cell lymphoma (DLBCL), including cases of primary mediastinal large B-cell lymphoma, was the most frequent subtype (52.8%). Follicular lymphoma (FL) was the second most frequent subtype (13.2%) followed by CLL/small lymphocytic lymphoma (CLL/SLL; 12.2%). The other B-cell subtypes were rare, including mantle cell lymphoma (MCL; 2.5%), marginal zone lymphoma of nodal or splenic type (MZL: 2.5%), high-grade B-cell lymphoma, Burkitt-like (1%) and precursor B-cell lymphoblastic leukemia/lymphoma (B-LBL; 0.5%). Among the T- and NK-cell neoplasms, the most frequent subtype was the combined group of peripheral T-cell lymphoma (PTCL; 6.1%), followed by precursor T-cell lymphoblastic leukemia/lymphoma (T-LBL; 3.6%) and extranodal NK/T-cell lymphoma, nasal type (3%). Among the 12 cases of PTCL, there were seven cases of PTCL, not otherwise specified (NOS), four cases of anaplastic large T-cell lymphoma and one case of angioimmunoblastic T-cell lymphoma.

The age of the patients ranged from eight to 92 years (median, 54 years). The median ages for the different lymphoma subtypes are shown in Table II. B-cell neoplasms occurred at a higher median age (55 years) than T-cell neoplasms (42 years). Among the B-cell neoplasms, the median age was lower in patients with high-grade lymphomas (50 years) compared to those with low-grade lymphomas (59.5 years). Patients with CLL/SLL had the lowest median age (57.5 years) among low-grade B-cell lymphomas, followed by FL (58.2 years) and MCL (64 years). Among T- and NK-cell lymphomas, the median age was lowest for T-LBL (25 years), followed by NK/T-cell lymphoma, nasal type (45.5 years) and PTCL (52.5 years).

The sex distribution of NHL in Algeria is shown in Table III. There were 109 (55.3%) males and 88 (44.7%) females, with a male-to-female ratio of 1.2. In 73% of the cases, the lymphomas were nodal, whereas 27% of cases were extranodal. The sex and biopsy site distribution of

Table III. Sex distribution of NHL in Algeria compared with Western Europe and North America.

Sex	Algeria, % (n)	Western Europe, % (n)	North America, % (n)		
Male	55,3 (109)	49.8 (272)	52.9 (210)		
Female	44.7 (88)	50.2 (274)	47.1 (187)		
M:F ratio	1.23	0.99	1.12		

NHL, non-Hodgkin lymphoma.

the most common NHL subtypes in Algeria are given in Table IV. The most common biopsy specimen was a lymph node, particularly in CLL/SLL (95%), FL (81%) and PTCL (80%). DLBCL was also most commonly diagnosed in a lymph node biopsy (71%), but also occurred in various extranodal locations including the spleen, head and neck, central nervous system, gastrointestinal tract and bone marrow. Precursor T-LBL was diagnosed by lymph node biopsy in 66% of cases, whereas NK/T-cell lymphoma, nasal type, was diagnosed exclusively on extranodal biopsies. MCL and PTCL occurred predominantly in men, with 80% and 75% of patients with these diagnoses being male, respectively.

Comparison of Algeria with Western Europe and North America

The relative frequencies of NHL subtypes in Algeria were compared to those in WEU and NA (Table I). There were no significant differences between Algeria and WEU or NA in the overall distribution of B-cell and T- or NK-cell lymphomas. The relative frequency of low-grade B-cell lymphoma was significantly lower (32.5%; p < 0.05) in Algeria compared to WEU (54.5%) and NA (56.1%), whereas the frequency of high-grade B-cell lymphoma was significantly higher in Algeria (54.8%) than in WEU (36.4%) and NA (34.3%). The high frequency of high-grade B-cell lymphomas in Algeria was almost entirely due to DLBCL (52.8%). Among the lowgrade B-cell lymphomas, Algeria had a higher frequency of CLL/SLL (12.2%) compared to NA (4.8%). The frequency of FL (13.2%) was significantly lower in Algeria than in either WEU (20.0%) or NA (33.6%). Furthermore, Algeria had a significantly lower frequency of low-grade FL (3.0%) compared

Table II. Median age (years) of the most frequent NHL subtypes in Algeria compared with Western Europe and North America.

	Algeria	Western Europe	North America
All B-cell lymphomas	55.0*†	61.0	66.0
Low-grade B-cell lymphomas	59.5	60.0	64
Chronic lymphocytic leukemia/small lymphocytic lymphoma	57.5 [†]	63.0	71.0
Follicular lymphoma, all grades	58.2	56.0	62.5
Low-grade	51.0	55.5	59.0
High-grade	60.5	60.0	68.0
Mantle cell lymphoma	64.0	63.0	64.0
Marginal zone lymphoma, nodal/splenic	67.0	66.0	48.0
High-grade B-cell lymphomas	50.0*1	62.0	68.0
Diffuse large B-cell lymphoma	49.0*f	62.5	69.0
All T-cell lymphomas	42.0	60.0	43.5
Peripheral T-cell lymphomas	52.5	61.0	46.0
Extranodal NK/T-cell lymphoma, nasal type	45.5	42.0	-
Precursor T-lymphoblastic leukemia/lymphoma	25.0	24.0	23.5
All lymphomas, B and T	54.0*†	61.0	65.0

NHL, non-Hodgkin lymphoma; NK, natural killer.

^{*}Significantly different from Western Europe, p < 0.05.
*Significantly different from North America, p < 0.05.

that region. These findings suggest that socioeconomic and environmental risk factors may be important in the etiology of FL [15,16]. Among the T- and NK-cell lymphomas, extranodal NK/T-cell lymphoma, nasal type, was more frequent in Algeria (3.0%) than in WEU (0.5%) and NA (0.0%), and T-LBL was also more common in Algeria (3.6%) than in WEU (0.9%), High frequencies of NK/T-cell lymphoma have been reported in Asian countries [1,13,14,17-19], as well as in the native population in some countries in Central and South America [2], and this lymphoma has been associated with Epstein-Barr virus infection [1,17,19]. The reasons for the differing frequencies of these lymphomas in Algeria are not well understood and will require further study.

With regard to age, T-LBL occurred in the youngest patients (median, 25 years), followed by extranodal NK/Tcell lymphoma, nasal type, which was seen predominantly in middle-aged adults (45.5 years). DLBCL also occurred at a relatively young age (49 years), significantly earlier than in WEU (62.5 years) and NA (69 years). Furthermore, Algerian patients with CLL/SLL (57.5 years) were significantly younger than those in NA (71 years). Other studies from the Mediterranean/Middle East (MME) [3,20-22] have reported a similar age distribution of NHL. Patients with T-LBL were among the youngest [3,21,22], whereas DLBCL also occurred at an earlier age (46-53 years) in all four studies from the Middle East [3,20-22]. However, CLL/SLL occurred at an older age (60-64 years) in Iran [20], Iraq [21] and Jordan [22] compared to Algeria, whereas in the United Arab Emirates [3] patients with CLL/SLL were much older (72 years), similar to NA. Remarkably, in Jordan [22], PTCL occurred at a much younger age (37 years) compared to Algeria. Overall, the age distribution of the different NHL subtypes in Algeria is similar to that of other developing countries in the region, with the major NHL subtypes occurring at an earlier age than in Western countries.

In this study we did not observe significant differences in the gender distribution of NHL between Algeria and WEU or NA. When compared with other MME studies [3,20-25], Algeria had a slightly lower male-to-female ratio (1.2:1), Of the other countries in the region, Jordan [22] had the lowest (1.5:1) and Egypt [24] had the highest (2.1:1) ratio.

In Algeria, NHL presented most commonly in lymph nodes, whereas 27% were extranodal. DLBCL presented in extranodal sites in 30% of cases, most commonly in the head and neck region. In comparison with other studies from MME, Algeria had a similar proportion of extranodal lymphomas as the United Arab Emirates (29%) [3], and a higher proportion than Iran (11.5%) [20]. Other studies [21-25] have reported higher frequencies of extranodal lymphoma (ranging from 36 to 54%) compared to Algeria. However, few studies [21,22] have reported the frequency of extranodal lymphomas by different lymphoma subtypes, Compared with studies from Iraq [21] and Jordan [22], Algeria had a lower number of extranodal lymphomas, especially DLBCL and PTCL.

We also compared the relative frequencies of the common NHL subtypes in Algeria with those from other countries in the MME (Table V) [3,20-27]. The frequency of CLL/ SLL was higher in Algeria than in most of the MME countries [3,21-27] with the exception of Iran [20], most probably due to study selection criteria. The relative frequency of DLBCL in Algeria was similar to the United Arab Emirates [3], Saudi Arabia [26], Kuwait [25] and Iraq [21], whereas other countries in the region [20,22-24,27] had a lower frequency. The frequency of FL in Algeria was intermediate compared to other countries in the MME, with Egypt [24], Jordan [22] and Lebanon [27] having higher FL frequencies than Algeria. MCL was uncommon in Algeria, similar to Saudi Arabia [26], Kuwait [25], Iran [20] and Iraq [21]. Extranodal NK/T-cell lymphoma, nasal type, was more common in Algeria than in other MME countries that reported this lymphoma subtype [22,23,26,27]. Finally, the relative frequency of T-cell lymphomas in Algeria was similar to Iraq [21] and Lebanon [27], but lower than in the United Arab Emirates [3], Turkey [23], Saudi Arabia [26], Kuwait [25] and Jordan [22].

In conclusion, the relative frequencies of the common NHL subtypes in Algeria are generally comparable to those in other countries in MME, and different from the Western world. The unusually high frequency of CLL/SLL observed

Table V. Distribution of the common NHL subtypes in the Mediterranean/Middle East.

Common NHL subtypes	Mediterranean/Middle East									
	Present study, Algeria	UAE [3]	Turkey [23]	Egypt [24]	Saudi Arabia [26]	Kuwait [25]	Iran [20]	Iraq [21]	Jordan [22]	Lebanon [27]
Chronic lymphocytic leukemia/small lymphocytic lymphoma	12.2	1,0	6.2	6.0	6.8	10.2	23.9	5.8	3.7	3.8
Follicular lymphoma, all grades	13.2	7.0	6.1	22.0	5.9	15.2	1.4	2.9	19.8 ·	20.2
Mantle cell lymphoma	2.5	NR	7.5	5.9	1.6	1,4	2.2	1.9	6.3	6.0
Diffuse large B-cell lymphoma	52.8	59.0	42.2	31.0	49.8	49.1	37.8	54.6	36.0	40.4
Extranodal NK/ T-cell lymphoma, nasal type	3.0	NR	0.6	NR	0.8	NR	NR	NR	1.1	0.5
T-cell lymphomas, all subtypes	9.7	17.1	15.6	5,8	18.3	18.0	4.2	9.3	16.5	8.7

NHL, non-Hodgkin lymphoma; NK, natural kilier; UAE, United Arab Emirates; NR, not recorded.

in Algeria is likely due to a difference in clinical practice. However, further, large-scale epidemiologic studies are needed to explain the many important differences observed in our study.

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