Valerie AFTIMOS1,2*, Sahar RASSI-ZANKOUL1, Zahraa NAJJAR1, Georges AFTIMOS3


ABSTRACT • The 2008 WHO classification is the gold standard for classifying hematopoietic neoplasms. Our study reviewed 1256 cases between the years 2010 and 2014. It aimed to establish a descriptive status of lymphoma cases in Lebanon. Hodgkin lymphomas (HL) accounted for 21% of all cases whereas non-Hodgkin lymphomas (NHL) accounted for 79%. In NHL, mature B-cell neoplasms accounted for 85% and mature T-cell neoplasms accounted for 9%. For mature B-cell neoplasms, the majority of cases (48%) were diffuse large B-cell lymphomas (DLBCL). Within T-cell lymphomas, anaplastic lymphoma (ALCL 40%) was the most prevalent. The distribution within subtypes confirmed the findings of two previous Lebanese studies. Our figures of HL are higher than in Eastern and Western countries. This could probably be related to EBV infection among other etiologies. Our NHL figures are close to the Western world. Westernization of the way of life of the Lebanese society could explain this result.

Keywords: hematopoietic neoplasms; lymphoma; Hodgkin lymphoma; non Hodgkin lymphoma; epidemiology

ABBREVIATIONS

HL: Hodgkin lymphoma
NHL: non Hodgkin lymphoma
DLBCL: diffuse large B-cell lymphoma
FL: follicular lymphoma
MZL: marginal zone lymphoma
ALCL: anaplastic T-cell lymphoma
PTL, NOS: peripheral T-cell lymphoma, unspecified

INTRODUCTION

The aim of a lymphoma classification is to provide a single language allowing communication between different parties involved in the management of the disease. The classification should be reproducible and clinically relevant.

Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHL) are classified separately. Two classifications of HL were proposed since 1925 versus more than 25 classifications of NHL. When seeing the diverse courses that could follow a NHL, with its different outcomes and survival as well as response to therapy, many classifications have been proposed and modified over time.

The term lymphoma was first used in 1858 and the first classifications were based on morphology (American Registry of Pathology in 1934, Robb-Smith in 1938, Gall and Mallory in 1942 and Jackson and Parker in 1939 and 1947).

The Classification for Hodgkin disease was proposed in a conference in Rye (NY) in 1966. It involves a modification of Lukes-Butler classification and divided Hodgkin disease into four histologic types: lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC) and lymphocyte depleted (LD) [1].

In 1966, Rappaport proposed a new classification based on morphology using cytology and architecture. In 1976, a modified Rappaport Classification was established [2,3].

1 National Institute of Pathology, Faculty of Medicine, Lebanese University, Rafic Hariri Campus, Baabda, Hadath, Lebanon.
2 Institut Jules Bordet, Service d’anatomie pathologie, Bruxelles, Belgique.
*Corresponding author: Valerie Aftimos, MD e-mail: vaftimos@gmail.com
In 1974, Kiel, as did Lukes and Collins, added immunophenotype to the morphological classification. Kiel classified lymphomas according to cell origin and differentiation. This classification was updated in 1992 [4]. Lukes and Collins proposed a scheme for B-cell types [5,6]. In 1982, the United States National Cancer Institute proposed the Working Formulation, which emphasized on grouping according to morphology and clinical prognosis, to translate among the various lymphoma classifications in use at the time (e.g., Rappaport, Lukes-Collins, and Kiel). It divided lymphomas into grades based on clinical behavior [7].

Prior to 1994, the Working Formulation was adopted in the United States, whereas the updated Kiel classification was used in Europe. In 1994, the Working Formulation and Kiel classifications were replaced with the Revised European-American Lymphoma (REAL) classification, which incorporated morphology, immunophenotype, genotype, normal cell counterpart, clinical presentation and course of the disease into subtype definitions [8].

The World Health Organization (WHO) classification introduced in 2001 and modified in 2008 was built on the REAL classification and is the current gold standard for classifying all hematopoietic neoplasms. The WHO system distinguishes hematologic malignancies according to cell lineage. Within the lymphoid neoplasms, morphology and immunophenotype distinguish HL from the NHL. Differentiation and additional morphologic, phenotypic, genotypic and clinical features distinguish among the NHL subtypes. The 2008 WHO classification also draws attention to early events in lymphomagenesis and defines several entities according to age and site in addition to biologic underpinnings. It defines as well borderline lesions. The WHO classification is found in Table I [9].

**TABLEAU I**  WHO CLASSIFICATION OF LYMPHOID NEOPLASMS [9]

**WORLD HEALTH ORGANIZATION OF LYMPHOID NEOPLASMS**

**PRECURSOR B- AND T-CELL NEOPLASMS**
- Precursor B-lymphoblastic leukemia/lymphoblastic lymphoma (precursor B-cell acute lymphoblastic leukemia)
- Precursor T-lymphoblastic leukemia/lymphoblastic lymphoma (precursor T-cell acute lymphoblastic leukemia)

**MATURE B-CELL NEOPLASMS**
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Plasma cell myeloma
- Monoclonal gammopathy of undetermined significance
- Solitary plasmacytoma of bone
- Extrasosseous plasmacytoma
- Primary amyloidosis
- Heavy chain diseases
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Lymphomatoid granulomatosis
- Mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma/leukemia

- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
MATERIAL AND METHODS

Our study is a cross-sectional study between the years 2010 and 2014, which aimed to establish a descriptive status of lymphoma cases in Lebanon. Our database came from a private pathology laboratory receiving cases from the entire Lebanese territory. The specimens consisted of biopsies of various lesions or excision of lymph nodes. They were fixed in formalin at 10% and embedded in paraffin. Charged slides were cut at 5 microns and stained by hematoxylin & eosin, Giemsa stain and reticulin stain. After a preliminary diagnosis by one pathologist, an immunohistochemical study was performed.

The cases were then classified following the 2008 WHO Classification shown in Table I. The panel of immunohistochemical stains used varied widely but the choice of antibodies was restricted and oriented by the morphological features to avoid the misinterpretation and the overlapping positivity. The most used antibodies were CD20, CD79a and PAX5 for identifying B-cell, CD3 and CD5 for T-cell along with CD23, CD21, TdT, Cyclin D1, Bcl2, Bcl6, LCA, OCT2, BOB1, LCA and Ki67. A second pathologist reviewed cases that were judged ambiguous or difficult.

1468 cases over five years diagnosed as lymphomas were selected. Those where the immunohistochemical study was not done (except for gastric MALT lymphomas, mycosis fungoid and Hodgkin, nodular sclerosing variant) or was inconclusive were excluded as well as relapses and secondary localizations, leaving us with a total of 1256 new cases. Data including the age and the sex of the patients, the localization of the biopsies taken and the lymphoma subtypes diagnosed were collected and then analyzed.

RESULTS

Within the final 1256 cases that we studied, we found 46.33% of women (581) and 53.67% of men (673), with an age varying between 1 and 98 years old and a mean age of 53 years old. For HL, two age peaks were found: one between 20-30 years (55 cases) and the second less prominent between 60 and 70 years of age (23 cases). Sex ratio and age distribution within the different lymphoma subtypes are found in Table II.

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<table>
<thead>
<tr>
<th>Subtype</th>
<th>Sex Ratio</th>
<th>Age</th>
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<tr>
<td></td>
<td>M/F</td>
<td>Min-Max</td>
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<tr>
<td>Hodgkin</td>
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<td>2 – 88</td>
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<tr>
<td>DLBCL</td>
<td>0.9</td>
<td>4 – 98</td>
</tr>
<tr>
<td>FL</td>
<td>0.9</td>
<td>15 – 86</td>
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<tr>
<td>MZL</td>
<td>1.3</td>
<td>5 – 89</td>
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<tr>
<td>MALT</td>
<td>0.8</td>
<td>7 – 87</td>
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<tr>
<td>ALCL</td>
<td>1.7</td>
<td>19 – 85</td>
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<tr>
<td>PTL, NOS</td>
<td>1.3</td>
<td>12 – 88</td>
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The incidence per year is shown in Fig. 1. Hodgkin lymphomas accounted for 21% (258 cases) whereas NHL accounted for 79% (996 cases). Within Hodgkin lymphomas, the nodular sclerosing variant accounted for most of the cases, summing up to 81% (210 cases) (Fig. 2a).

When considering NHL, mature B-cell neoplasms account for 85% (853 cases), mature T-cell neoplasms account for 9% (87 cases). The remaining 6% are distributed between precursors lymphoid neoplasms, composite lymphomas and grey zone lymphomas (Fig. 2b). For mature B-cell neoplasms, the majority of cases 48% (406 cases) are diffuse large B-cell lymphomas (DLBCL), followed by follicular lymphomas (FL) (16%, 136 cases), and mucosa-associated lymphoid tissue (MALT) and marginal zone lymphoma (Mzl) accounting for 9% each (75 cases of MALT and 74 cases of Mzl). To note, 12 cases of composite lymphomas were DLBCL and FL lymphomas (Fig. 2c). When considering mature T-cell neoplasms, the majority of cases are distributed between anaplastic lymphomas (ALCL 40%, 35 cases) and peripheral T-cell lymphomas, NOS (PTCL, NOS 34%, 30 cases) (Fig. 2d).

HL, MZL, ANCL and PTCL, NOS showed a male predominance while DLBCL, FL and MALT showed a slight female predominance. NHL’s mean age varied from 50- to 60-year-old while HL arise in younger people with a mean age around 37-year-old (Table II). Concerning localization, 54% of lymphomas were nodal (680 cases). The extra-nodal localization was mainly found in the stomach (8.7%) followed by the bone marrow (6.6%) with 18.3% of miscellaneous locations (Fig. 3).

**DISCUSSION**

When comparing to previous studies, we will direct our attention first to the two largest Lebanese studies covering lymphoid malignancies: Sader-Ghorra C. et al. [10] and Otrock ZK et al. [11]. Our study covers 1256 new cases whereas the two other studies covered 502 and 272 new cases respectively. Our rates of HL and NHL are in
between both results: we found 21% HL vs. 79% NHL, whereas Sader-Ghorra C. et al. [10] found 24% HL vs. 76% NHL and Otrock ZK et al. [11] 32.7% HL vs. 67.3% NHL. Nodular sclerosing variant was predominant in both our study and Otrock ZK et al.’s [11]. Among NHL, all studies demonstrated that mature B-cell lymphomas represented the largest portion with very close results while mature T-cell lymphomas represented 9% in all three studies. Within mature B-cell lymphomas, all three studies showed a predominance of DLBCL with close results followed by FL, which was estimated at 17% in our study but at a higher proportion in the two other studies (20% in Sader-Ghorra C. et al. [10] and 23% in Otrock ZN et al. [11]).

Worldwide, the incidence of lymphoma seems to be increasing and this is mainly true for the incidence of lymphoma in the Western world such as the US and Europe [12,13]. This is also true for Lebanon [14]. While NHL ranks 12th in incidence in Europe [13], the incidence in Lebanon mirrors that of the US: 5th in men and
4\textsuperscript{th} in women in Lebanon [14] and 6\textsuperscript{th} in men and women in the US [12]. When comparing to lymphoid malignancies around the world, HL (21\% in our study) seems more frequent than in Western and Far Eastern countries (11.6\% in the US [15], 14.4\% in the UK [16], 5.19\% in China [17] and 5.9\% in Japan [15]), and approaches the numbers in Turkey (17\%) [18] and in Iraq (24\%) [19]. Saudi Arabia has the highest rate with 32\% [20]. In NHL, T-cell lymphomas are more frequent in our series (9\%) than in Western countries (5.3\% in the UK [16]) but less frequent than in Far Eastern countries (16.51\% in China [17]). We found that Turkey (8\%) [18], Iraq (9\%) [19] and Algeria (12.7\%) [21], had close figures.

HL seems to be higher in Lebanon versus the rest of the world. In fact, a study by GLOBOCAN 2012 showed that Israel and Lebanon seemed to have the highest incidence of HL around the Mediterranean Basin [22]. The etiological factors involved in the pathogenesis of HL are multifactorial and include both genetic and environmental risk factors. These risk factors include EBV infection. EBV-positivity was found to be 90\% in Greece, 61.5\% in Turkey, 50\% in Egypt, 48\% in Italy and 30\% in Israel [23-27]. In Lebanon, the study by Otrock ZK et al. [11] showed that 39 out of 43 patients having HL had positive EBV IgG antibodies. Furthermore, 54.5 \% of EBV seropositive HL cases were positive for latent EBV expression using in situ hybridization for EBER. These findings are a proof that further exploration of the relationship between EBV and HL needs to be investigated.

Another association was found with tuberculosis. It seems that HL’s incidence is higher in areas where tuberculosis is endemic. Tuberculosis precedes, is concomitant or follows HL [26,28,29]. In Lebanon, the declared prevalence of tuberculosis was estimated at 12/100,000 inhabitants in 2009 [30]. In 2011, the estimated prevalence was 19/100,000 in Lebanon. Since then, 630 new cases were declared in 2012 and 689 new cases in 2013, including non-Lebanese residents [31], showing that incidence of tuberculosis in Lebanon seems to be on the rise.

As shown by Roman E. and Smith A., we also had a bimodal age distribution for HL [32]. Our first peak was in young adults (20-30 years) and the second in the elderly (60-70 years).

Concerning NHL, the most common subtype in the current study was found to be DLBCL with a rate of 40.7\%. This rate is close to the one found in the UK (40.9\%) [16] and in France (41\%) [33] and is lower than the one found in Algeria (52.8\%) [21], Saudi Arabia (51\%) [20], Iraq (52.2\%) [19] and China (53.5\%) [17]. FL is close to Western incidence with a rate of 13.6\% (UK 15.9\% [16], US 17\% [15]. This rate is lower in Iraq (2.9\%) [19] and in Saudi Arabia (7\%) [20] but almost similar in Algeria (13.2\%) [21].

Numbers in the current study approach the Western countries statistics. DLBCL and FL are the most common subtypes in our study as well as in the Western countries [34]. However T-cell lymphoma rates seem to be halfway between the Eastern and the Western world, considering that rare T-cell neoplasms are more common in Asia than in the rest of the world [34]. It seems to be related to the HTLV-1 virus, which is more common in Japan and the Caribbean and rare in Europe and the USA [35]. Genetic factors play an important role in the etiology of NHL: chromosomal translocations have been observed in up to 90\% of NHL cases [36,37]. However, the uniform rise of NHL throughout the world implicates the role of environmental agents [34]. Some studies have shown that higher consumption of meat and dairy products is associated with an increased risk of NHL, whereas higher consumption of vegetables and fruits reduces NHL risk [38,39]. Particularly for DLBCL, an association with a high body mass index has been found [40]. FL on the other hand has been linked to tobacco smoking, as the latter appears to induce the BCL2 translocation (14, 18) found in FL [41]. These environmental agents are found mostly in the Western world but also in Lebanon as westernization of the way of life occurs and could explain our numbers.

CONCLUSION

Despite the numerous studies conducted to search for an etiology for lymphomas, the latter remain poorly understood. However, it seems that westernization may play an important part in explaining the distribution of the different subtypes in Lebanon. This would explain the similar numbers in non-Hodgkin B-cell lymphomas. Lebanon, being a Mediterranean country, the relationship to EBV virus can explain the higher figures of HL in the current study.

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CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interests regarding this paper.

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