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RESEARCH

A Collaborative Nationwide Lymphoma Study in Lebanon: Incidence of Various Subtypes and Analysis of Associations with Viruses

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Abstract Incidence of various Hodgkin (HL) and non-Hodgkin lymphoma (NHL) subtypes and association with viruses in Lebanon are not known. We undertook a nationwide study of 272 patients diagnosed with lymphoma in 2007. HL comprised 32.7 % (n=89) of cases while NHL represented 67.3 % (n=183). Consistent with the literature, nodular sclerosis was the most predominant HL subtype (n=57/89). Among NHL, B-cell NHL represented 88 % (n=161/183), T-cell NHL 9 % (n=17/183), whereas in 2.7 % it was not classifiable. The B-cell NHL comprised predominantly diffuse large B-cell lymphoma (46 %) and follicular lymphoma (23 %). 81 cases were reviewed by a panel of pathologists with 87.6 % concordance rate. Serology was negative for hepatitis C in 122 tested cases. HIV was positive in 2 cases. Two adult T-cell leukemia/lymphoma were HTLV-I positive. EBV IgG were positive in 88.5 % of cases. 38 EBV seropositive cases [27 NHL (24 B-cell, 3 T-cell) and 11 HL] were studied for EBV genome expression using EBV-encoded

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RNA (EBER)-in situ hybridization. EBER expression was positive in 8 (21 %) cases (6 HL, 2 T-cell NHL). The distribution of lymphoma subtypes in Lebanon appears similar to that of Western countries. The high rate of EBV positivity in HL and T-cell lymphoma by EBER deserves further investigation.

Keywords Lymphoma · Incidence · Subtypes · Viruses · EBV · Lebanon

Introduction

Lymphomas represent a diverse, yet closely related group of neoplasms originating in the lymphopoietic system [1]. This group is classified into two major categories: Non-Hodgkin lymphoma (NHL), which corresponds to 85–89 % of cases, and Hodgkin lymphoma (HL), accounting for the remaining 11–15 % of all malignant lymphomas [2–4]. The etiologic factors underlying the two categories of lymphomas are not entirely known although several studies have identified predisposing factors including primary and acquired immunosuppression, acquired chromosomal translocations, human immunodeficiency virus (HIV), human T-lymphotropic virus type I (HTLV-I), Helicobacter pylori, hepatitis C virus (HCV), and human herpes virus 8 (HHV-8), among others [5–9].

Several studies have reported a steep increase in age-adjusted incidence of and mortality from NHL in Europe and North America, especially in 1990's with an annual increase in incidence of nearly 3 % [10]. This increase in NHL incidence and mortality persisted until the mid-1990's, it stabilized and then declined in the subsequent decade [11, 12]. The earlier dramatic increase in NHL incidence was attributed in part to emergence of HIV and acquired immunodeficiency syndrome (AIDS) coupled with diagnostic advancements [13–15].

The incidence patterns of all subtypes of lymphoma vary according to gender, race and geographic distribution, providing some evidence of etiologic as well as epidemiologic heterogeneity by disease subtype [7, 16, 17]. According to the IARC (World Health Organization International Agency for Research on Cancer), NHL rate is higher in developed countries than in Africa and Asia [18]. There is higher predominance in males, as well as higher rates in whites compared to African Americans. Moreover, there is an increase in incidence with age across most lymphoma subtypes [1, 16]. In regards to HL, its incidence remains lower than NHL and appears to have decreased even further (approximately 16 %) after 1970 [19, 20].

Most of available data regarding the relative distribution of the various lymphoma subtypes and their potential association with viruses has been reported in several Western and Asian countries. Such association is less known for developing countries, particularly in the Middle East. We conducted this prospective study that assesses the incidence of particular subtypes and evaluates possible associations with various viruses in adult patients with newly diagnosed lymphomas in Lebanon.

Patients and Methods

We conducted a prospective epidemiologic study that included adult patients (≥18 years) diagnosed with lymphomas during the year of 2007 across several hospitals in Lebanon. This comprehensive collaborative nationwide study was undertaken in collaboration with the Lebanese Society of Hematology and Blood Transfusion, the Lebanese Society of Anatomic Pathology, the Lebanese Society of Medical Oncology and the Lebanese Cancer Society. The study was approved by the institutional review board of the American University of Beirut Medical Center (AUBMC). Signed informed consents were obtained from participating subjects who consented to undergo phlebotomy for viral serology testing.

Adult patients with a histologically confirmed diagnosis of lymphoma during 2007 were eligible for enrollment. Clinical and pathology data were collected in a data sheet form which comprised available pathology material for each subject which was reviewed according to the 2001 World Health Organization (WHO) classification system [21] by a panel of expert pathologists.

Peripheral blood (20 ml) was withdrawn for serology testing for the following: HCV, HIV, EBV, and HTLV-I. Blood was collected and the separated serum was aliquoted and cryopreserved at −20 °C. After the completion of blood sample collection, serum aliquots were thawed and tested for viral serology in panels. Serology testing was conducted at the Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center using manufacturer's user guide for each assay. The presence of anti-HCV antibodies was done using microparticle enzyme-linked immunoassay (AxSYM HCV version 3.0, Abbott laboratories, IL, USA). Similarly, detection of antibodies to HIV type 1 and type 2 (HIV-1/HIV-2) and HIV p24 was done using microparticle enzyme-linked immunoassay (AxSYM HIV Ag/Ab Combo; Abbott Park, IL, USA). EBV serology testing was done using the microplate enzyme-linked immunosorbent assay (ELISA) test kit (EBV-CA IgG, Euroimmun, Germany) that detects IgG antibodies against EBV capsid antigen (EBV-CA). Detection of antibodies against human T-lymphotropic virus types I and II (HTLV-I and HTLV-II) was done using the Abbott-Murex HTLV I/II GE 80/81 enzyme immunoassay (EIA) (Murex Diagnostics, Dartford, UK).

The presence of EBV genome was further investigated using EBV-encoded RNA (EBER)-in situ hybridization on a cohort of EBV-seropositive lymphoma cases. The testing

was carried out on formalin-fixed paraffin-embedded samples according to the manufacturer's protocol (Ventana Medical Systems, Tucson, AZ, USA). EBER testing was done at "Institut National de Pathologie" in Lebanon.

Results

Throughout 2007, 272 adult patients (≥18 years) diagnosed with lymphoma were recruited across Lebanon. There were 138 (50.7 %) males and 134 (49.3 %) females. The median age at diagnosis was 52 (n=252, range 18–71) years. These patients were treated and followed up by 32 hematologists/oncologists distributed across 40 medical centers in Lebanon.

Pathology

Eighteen pathologists working at various academic and community-based medical centers rendered the primary diagnosis of lymphoma. Initial pathology diagnoses of the 272 enrolled cases were as follows: 183 (67.3 %) NHL and 89 (32.7 %) HL. The NHL comprised 161 (88 %) B-cell lymphomas, 17 (9.3 %) T-cell lymphomas, and 5 (2.7 %) unclassified lymphomas.

B-cell lymphomas comprised 74 (46 %) diffuse large B cell lymphoma (DLBCL), 37 (23 %) follicular lymphoma (including one case of transformation to DLBCL), 13 (8.1 %) marginal zone/mucosa-associated lymphoid tissue (MALT) lymphoma, 11 (6.8 %) mantle cell lymphoma, 7 (4.3 %) small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL), 2 (1.2 %) lymphoblastic lymphoma, and 17 (10.6 %) B-cell lymphoma not otherwise specified (NOS). The T-cell lymphomas included 7 peripheral T-cell lymphoma NOS, 4 anaplastic T cell lymphoma, 2 lymphoblastic lymphomas, 2 adult T cell leukemia/lymphoma (ATL),1 angioimmunoblastic T cell lymphoma, and 1 natural killer (NK) cell lymphoma. The HL cases included 57 (64.1 %) nodular sclerosis, 4 (4.5 %) mixed cellularity, 5 (5.6 %) lymphocyte-predominant, 1 (1.1 %) lymphocyte-rich, 14 (15.7 %) classical HL NOS, and 8 (9 %) unclassified HL.

Eighty-one cases were reviewed by a pathology panel. Nine pathologists from various centers involved in this study participated in the review of the surgical and biopsy slides. The overall concordance rate was 87.6 % (71/81). There was discordance in 6 (7.4 %) cases whereas 4 cases were considered equivocal on revision. The discordant cases comprised 3 originally diagnosed DLBCL which were revised to high-grade follicular lymphomas, 1 DLBCL which was revised to SLL, 1 low-grade lymphoma revised to DLBCL, and 1 lymphoblastic lymphoma revised to DLBCL.

Virology Results

Blood was obtained from 122 patients. Serology was negative for HCV in all tested cases. HIV was positive in 2 cases (1 NHL - MALT type, 1 HL - mixed cellularity). The two ATL cases tested positive for HTLV. EBV IgG antibodies were positive in 108 (88.5 %) cases (69/79 NHL, 39/43 HL). Furthermore, 38 EBV seropositive cases (27 NHL: 24 B-cell type and 3 T-cell type; 11 HL) were studied for latent EBV using in situ hybridization for EBER. EBER expression was positive in 8 (21 %) cases corresponding to 54.5 % of EBV seropositive HL cases (4 nodular sclerosis, 1 lymphocyte-predominant, 1 classical) and 66.7 % of EBV serpositive T-cell NHL (1 angioimmunoblastic and 1 peripheral T-cell lymphoma NOS).

Discussion

This study represents a collaborative effort among community and academic-based medical centers in Lebanon to evaluate the incidence in adults of various lymphomas diagnosed in 2007; and to evaluate possible associations with viruses.

We show that the crude incidence of adult lymphoma is 9.5 cases per 100,000 population. A previous study [22] reported a crude incidence of lymphoma of approximately 7.9 cases per 100,000 population for an estimate of 3.3 million of the Lebanese population (at the time a total of 174 lymphoma cases were registered). However, such study included both adult and pediatric subjects. Accordingly, the adjusted incidence in adult population (≥18 years) was probably less than 6 cases per 100,000. Consistent with reports from other parts of the world, our results demonstrate an increase in incidence of lymphomas over the last 10 years. These findings need to be studied at a larger scale taking into account potential factors that might have contributed to this increase.

Our observed distribution between NHL and HL is comparable to other Arab countries [23–27]. In contrast, data from Western countries show an 11–15 % of the lymphomas being of the Hodgkin type [2–4]; whereas one-third of our cases were HL. With regard to the immunophenotypic distribution of NHL, T-cell lymphomas were uncommon in our population (9.3 %). Our proportion of T-cell lymphomas appears lower than in other Arab countries, namely Jordan, Kuwait and Saudi Arabia [25, 26, 28] (Table 1) and well below the incidence observed in some Asian countries, namely Japan, Korea, and China where it is reported to range between 16 % and 40 % [29–32].

Among the B-cell lymphomas, DLBCL was the most common subtype in our study (46 %), followed by follicular lymphoma (23 %). We found that the incidence of DLBCL is comparable to that reported by Saudi Arabia and Jordan [25,

Table 1 Comparative distribution of NHL cases by immunophenotype and histological subtypes using the WHO classification in Middle East countries and in the USA

Author, year of publication (country)	*N*	NHL subtype – N (%)
Haddadin 2005 (Jordan) [26]	272	B-cell – 224 (82.4) DLBCL – 98 (43.7) Follicular – 54 (24.1) MZ/MALT – 9 (4) Mantle – 17 (7.6) SLL/CLL – 10 (4.5) T-cell – 48 (17.6)
Ameen et al. 2010 (Kuwait) [33]	738	B-cell – 600 (81.2) DLBCL – 345 (57.5) Follicular – 112 (18.7) MZ/MALT – 20 (3.3) Mantle – 10 (1.7) SLL/CLL – 75 (12.5) T-cell – 114 (14.2) Null-cell – 24 (3.3)
Temmim et al. 2004 (Kuwait) [28]	821	B-cell – 655 (79.8) DLBCL – 481 (73.4) Follicular – 38 (5.8) MZ/MALT – 78 (11.9) Mantle – 2 (0.3) SLL/CLL – 9 (1.4) T-cell – 166 (20.2)
Abdel-Fattah et al. 2007 (Egypt) [71]	2638	B-cell – 1893 DLBCL – 818 (31) Follicular – 580 (22) MZ/MALT – 159 (6) Mantle – 155 (5.9) SLL/CLL – 158 (6) T-cell – 153 (5.8) Others – 249 (9.4) Unknown – 343 (13)
Akhtar et al. 2009 (Saudi Arabia) [25]	251	B-cell – 205 (81.6) DLBCL – 125 (61) Follicular – 15 (7.3) MZ/MALT – 11 (5.4) Mantle – 4 (2) SLL/CLL – 17 (8.3) T-cell – 46 (18.4)
Wu et al. 2009 (United States) [72]	30, 444	B-cell – 23,737 (78) DLBCL – 12,195 (51.4) Follicular – 2,314 (9.7) MZ/MALT – 3,726 (15.7) Mantle – 764 (3.2) SLL/CLL – 989 (4.2) T-cell – 4,749 (15.6) Unclassified – 1,958 (6.4)
Current study (Lebanon)	183	B-cell – 161 (88) DLBCL – 74 (46) Follicular – 37 (23) MZ/MALT – 13 (8.1) Mantle – 11 (6.8) SLL/CLL – 7 (4.3) T-cell – 17 (18.4) Unclassified – 5 (2.7)

26]. Yet, it was lower than in the United Arab Emirates and Kuwait [23, 33] (Table 1).

Nodular sclerosis comprised the major histological subtype of HL in our study (64.1 %). This high rate is comparable to that in some Arab countries as well as the USA [34, 35]. Conversely, Bahrain has a predominance of mixed cellularity HL [27]. The results from Kuwait are different based on two reports; for instance, Maker et al. [36] reported a predominance of mixed cellularity (45.5 %) followed by nodular sclerosis (37.3 %), while Al-Shemmari et al. [37] described a predominance of nodular sclerosis (46.4 %) followed by mixed cellularity HL (30 %) (Table 2).

Accurate diagnosis and subtyping of lymphoma remain a challenge. According to Procter et al. the discordance rates have decreased. They attributed this reduction to the pathologists' familiarity with the WHO classification [38]. Nevertheless, the discordance rates between the original pathology and the review diagnosis remained substantially high, up to 28 % [38, 39]. The diagnostic concordance rate among our pathology panel was 87.6 %, a rate which compares favorably to other reports in the literature.

The association between HCV and NHL was first reported in 1994 [40, 41] and was later confirmed in many studies. In a meta-analysis of 15 case–control studies and 3 prospective studies, the pooled relative risk of all NHL among HCV-positive individuals was 2.5 (95 % CI, 2.1–3.0) [42]. However, considerable heterogeneity was found among studies. One of the heterogeneity contributors is geographic area; the relative risk was significantly higher in geographic areas where HCV was prevalent. In these studies, however, no association could be observed between HCV and NHL [43, 44]. None of our lymphoma patients was seropositive for HCV by enzyme-linked immunoassay. These results are consistent with data from a previous study from Lebanon showing negative HCV serology in Lebanese patients with NHL [45]. Such findings are not surprising knowing that the prevalence of HCV antibodies in the country is markedly low (0.16 %) [46].

HTLV-I is the causative agent of ATL, an aggressive malignancy of mature activated T cells that is found in endemic

Table 2 Comparative distribution of HL cases by histological subtypes using the WHO classification in Middle East countries and in the USA

Author, year of publication (country)	*N*	HL subtypes – N (%)
Haddadin 2005 (Jordan) [26]	75	Lymphocyte predominant – 5 (6.7) Lymphocyte rich – 4 (5.3) Mixed cellularity – 19 (25.3) Nodular sclerosis – 27 (36) Lymphocyte depleted – 2 (2.7) Classic HL (NOS) – 18 (24)
Almasri et al. 2004 (Jordan) [67]	56	Lymphocyte predominant – 6 (10.7) Mixed cellularity – 24 (42.8) Nodular sclerosis – 24 (42.8) Lymphocyte depleted – 2 (3.6)
Makar et al. 2003 (Kuwait) [36]	134	Lymphocyte predominant – 9 (6.7) Mixed cellularity – 61 (45.5) Nodular sclerosis – 50 (37.3) Lymphocyte depleted – 4 (3) Lymphocyte rich – 4 (3) Unclassified – 6 (4.5)
Al-Shemmari et al. 2004 (Kuwait) [37]	140	Lymphocyte predominant – 24 (17.1) Mixed cellularity – 42 (30) Nodular sclerosis – 65 (46.4) Lymphocyte depleted – 3 (2.1) Unclassified – 6 (4.3)
Akhtar et al. 2009 (Saudi Arabia) [25]	60	Lymphocyte predominant – 5 (8.3) Lymphocyte rich – 4 (6.7) Mixed cellularity – 9 (15) Nodular sclerosis – 41 (68.3) Lymphocyte depleted – 1 (1.7)
Al-Kuraya et al. 2006 (Saudi Arabia) [34]	93	Lymphocyte predominant – 5 (4.9) Mixed cellularity – 9 (8.8) Nodular sclerosis – 71 (69.6) Lymphocyte depleted – 3 (2.9) Unclassified – 5 (13.7)
Castella et al. 2001 (United Arab Emirates) [23]	85	Lymphocyte predominant – 11 (13) Mixed cellularity – 26 (31) Nodular sclerosis – 36 (42) Lymphocyte depleted – 5 (6) Unclassified – 7 (8)
Allemani et al. 2006 (United States) [35]	3442	Lymphocyte predominant – 220 (6.4) Mixed cellularity – 675 (19.6) Nodular sclerosis – 2124 (61.7) Lymphocyte depleted – 69 (2) Unclassified – 354 (10.3)
Allemani et al. 2006 (Europe) [35]	6, 726	Lymphocyte predominant – 639 (9.5) Mixed cellularity – 1352 (20.1) Nodular sclerosis – 3087 (45.9) Lymphocyte depleted – 323 (4.8) Unclassified – 1325 (19.7)
Current study (Lebanon)	89	Lymphocyte predominant – 5 (5.6) Lymphocyte rich – 1 (1.1) Mixed cellularity – 4 (4.5) Nodular sclerosis – 57 (64.1) Classical HL (NOS) – 14 (15.7) Unclassified – 8 (9)

regions such as southern Japan, the Caribbean, Central and South America, Romania, and northern Iran [47, 48]. We had two cases of HTLV-I positive ATL, which were previously reported as the first cases from Lebanon [49]. The exact prevalence of HTLV-I in the Lebanese population is not known, however it is currently being investigated. The association between HIV and lymphoma has been examined in several studies with a risk of developing lymphoma above 300-fold [50, 51]. HIV was one of the factors contributing to the rise in NHL incidence in the 1970s–1990s [52]. Two of our cases were HIV positive; however, we do not know the temporal association between HIV and the disease in these cases. In addition, the lymphoma subtypes of the HIV positive cases are not commonly known to be associated with HIV.

EBV has been implicated in the development of a wide spectrum of B cell lymphoproliferative disorders including Hodgkin lymphoma, Burkitt lymphoma, peripheral T-cell and angioimmunoblastic T-cell lymphomas [53–55]. EBV genomes have been identified within the Reed-Sternberg (RS) cells of HL in up to 40–50 % of cases [56]. In addition, more patients with HL than expected have high levels of antibodies against EBV capsid antigen [57]. In EBV positive cases, lymphoma cells express EBV latent membrane protein-1 (LMP-1) [58]. The EBV genome is commonly detected by either LMP-1 immunohistochemistry or EBV-encoded RNA (EBER) in situ hybridization in RS cells [59–61]. Since EBV is ubiquitous in the general population with the majority of individuals being seropositive, the serum EBV IgG antibodies or the virus detection by PCR cannot imply a role of the virus in the pathogenesis of lymphoproliferative disease [62]. It is rather imperative to prove the presence of EBV or its molecules in lymphoma cells. In our study, EBV IgG antibodies were positive in the majority of lymphoma cases (88.5 %). However, EBER testing was positive in 54.5 % of seropositive positive HL cases and in 66.7 % of seropositive T-cell NHL. Of the 6 EBER positive HL cases, 4 had nodular sclerosis subtype, 1 lymphocyte-predominant, and 1 classical HL. The two EBER positive T-cell NHL consisted of 1 angioimmunoblastic and 1 peripheral T-cell lymphoma, NOS. These finding confirm a strong association of EBV with HL and T-cell lymphoma. Worldwide there is a wide variation

in the frequency of EBV expression in HL as EBV expression ranged from 27 % in Sweden [63] to 94 % in Peru [64]. Our findings of a high EBV frequency in nodular sclerosis HL are contrary to other studies from developing countries where EBV was more frequent in mixed-cellularity subtypes [65–67], and probably result of the overwhelming predominance of nodular sclerosis in patients with HL in Lebanon. This variation in EBV expression needs to be studied at a larger scale in Lebanon before reaching final conclusions. Another point of controversy is the relation between EBV antibodies and its expression in tumor cells. While most studies did not find a link between the EBV serology and EBV tumor expression [68, 69], Axdorph et al. reported a positive correlation between EBV antibodies (IgG EA-R, early antigen restricted) and EBV positive HL [70].

In conclusion, the distribution of lymphoma subtypes in Lebanon appears comparable to Western countries. The observed diagnostic concordance rate of 87.6 % is particularly noteworthy and provides a sense of reassurance pertaining to the quality of histologic readings. Viral serology did not reveal specificities except for a high EBV positivity in HL and T-cell lymphoma by EBER which deserves further evaluation.

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Conflict of Interest Statement The other authors have no conflicts of interest to disclose.

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