

Malignant lymphoma in Jordan: A retrospective analysis of 347 cases according to the World Health Organization classification

William J Haddadin

BACKGROUND: Most studies describing the subtypes of lymphoma in Jordan were carried out in the 1980s at a time when immunohistochemical facilities were unavailable. Using a database established after immunohistochemical studies were introduced, we determined the frequency of the various types of nodal and extranodal lymphomas in the adult and paediatric Jordanian population. We also assessed the incidence of bone marrow involvement at the initial presentation for each lymphoma type.

METHODS: A retrospective analysis of the histopathological subtypes of various lymphomas was conducted on all primary lymphoma cases diagnosed during a 3-year period between January 2001 and December 2003.

RESULTS: Of 347 patients included in the study, 78.4% had non-Hodgkin's lymphoma (NHL) and 21.6% had Hodgkin's lymphoma (HL). In the NHL group, diffuse large B-cell lymphoma was the most common (28.2%) followed by follicular lymphoma (15.6%). In the HL group, the nodular sclerosis variant was the most frequent (7.8%) followed by the mixed cellularity type (5.5%). Of all the lymphoma cases, the highest incidence of marrow involvement was seen in patients with lymphoplasmacytic lymphoma. Forty-nine patients were children (age <15 years) in whom Burkitt's lymphoma (15 cases) and HL (14 cases) were the commonest subtypes. One-hundred six patients with primary extranodal lymphomas (ENL) accounted for 30.5% of all lymphomas.

CONCLUSIONS: There is a higher incidence of NHL in Jordan compared with other series in the Middle East. Among the various lymphomas, diffuse large B-cell lymphoma is the most commonly encountered lymphoma in adults. Burkitt's lymphoma and Hodgkin's disease are the most frequent childhood lymphomas, followed closely by lymphoblastic lymphoma.

From the King Hussein Medical Centre, Department of Pathology, Amman, Jordan

Correspondence:
W.J. Haddadin, MRCPATH
Consultant Pathologist
City Hospital NHS Trust
Department of Pathology
Dudley Road
Birmingham B18 7QH
United Kingdom
williamhaddadin@swbh.nhs.uk

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Malignant lymphomas occur in all races, but the relative incidence of different subtypes varies in different parts of the world and in different races. Over the past ten years several studies have determined the various patterns of lymphoma in several parts of the world using either the Revised European-American Lymphoma¹ (REAL) or the World Health Organisation² (WHO) classification of lymphomas. Well-documented series have been reported from North America and Europe³⁻⁵ to the Far East in countries such as Thailand, Japan, and South Korea.⁶⁻⁹ In the Middle East several studies have characterised the pattern of lymphomas in this part of the world.¹⁰⁻¹⁵ These studies have found diffuse large B-cell lymphoma to be the most commonly encountered lymphoma, a finding similar to studies in the Western countries and the Far East. There have been few studies

on the various subtypes of lymphoma encountered in the Jordanian population.¹⁶⁻²⁰ With the exception of a very few recent studies,²⁰ most studies were carried out in the 1980s at a time when immunohistochemical facilities were unavailable. This study documents the pattern of lymphoma in Jordan using ancillary immunohistochemical studies in addition to the standard haematoxylin and eosin (H&E) stains performed on paraffin embedded tissue in conjunction with available clinical information.

Methods

King Hussein Medical Center is the largest multidisciplinary medical institution in Jordan. It is one of the main referral hospitals in Jordan with a capacity of around 1000 beds. The pathology department receives on average 13 000 pathology and cytopathology specimens every year. Of these, 2000 malignant cases are diagnosed annually. Lymphomas are the second most common malignancy diagnosed every year, preceded only by lung carcinoma as the most frequent malignant tumour.

A total of 347 (298 adults and 49 paediatric) cases of primary malignant lymphomas were collected from our database over a 3-year period starting on January 2001, which corresponds to the starting period when immunohistochemical studies were introduced at the pathology department. Plasma cell dyscrasias and leukaemia were excluded from this study. All these lymphoma cases belonged to patients who were diagnosed and treated at this centre. Myself and three other pathologists initially made the diagnoses. All cases were reviewed by myself and classified according to the WHO classification of lymphoid neoplasms.² There were a few cases in which the diagnoses needed to be changed, following discussions and further studies, until a consensus was established with the relevant pathologist. Tissue sections from paraffin embedded tissue on soft tissue and decalcified bone marrow specimens were examined by standard H&E stain and a panel of immunohistochemical markers using the streptavidin-biotin peroxidase method. The panel included antibodies against CD45 (LCA), CD45RO, CD79, CD20, CD10, CD23, CD3, CD5, CD43, CD56, CD8, CD4, CD30, CD15, CD34, EMA, BCL-2, TdT, Ki67, ALK1, and kappa, and lambda light chains. These antibodies were employed as was judged necessary from the H&E stained sections.

The data on gender, age, and site of involvement were extracted from the clinical histories in each case. Data from bone marrow trephine biopsies were

also collected from the computer records. The few cases in which a diagnosis of lymphoma was established from the trephine marrow biopsy were also included in the study.

Results

Of the 347 patients with lymphoma, there were 272 cases (78.4%) of non-Hodgkin's lymphoma (NHL) and 75 cases (21.6%) of Hodgkin's lymphoma (HL).

Non-Hodgkin's lymphoma Among the 272 patients with NHL, 165 patients were males (60.7%) and 107 were females (39.3%). The age of the patients ranged from 3 to 91 years. A total of 173 cases (63.6%) were nodal and 99 cases (36.4%) were extranodal in origin. The most frequent nodal location was the cervical region (68 cases, 25%), followed by the axillary nodes (37 cases, 13.6%), the inguinal nodes (20 cases, 7.4%), the mediastinal nodes (13 cases, 4.8%), abdominal nodes (10 cases, 3.7%), and others. The most frequent extranodal location was the stomach, with 21 cases accounting for 21.2% of all extranodal NHL.

Among all cases of NHL, B-cell neoplasms were the predominant type, accounting for 82.4% of all cases (Table 1). Of the B-cell tumours, diffuse large B-cell lymphoma was the commonest subtype (98 cases, 43.8%). There were 2 cases of diffuse large B-cell lymphoma showing CD30 co-expression. The second most frequent B-cell NHL was follicular lymphoma with (54 cases, 24%). Among the follicular lymphomas grade 2 was the commonest subtype (23 cases), followed by grade 3 (18 cases), and grade 1 (13 cases). Burkitt's lymphoma was the third commonest B-cell lymphoma with 17 cases (7.6%), 2 of which were nodal and 15 of extranodal origin. Among all 272 NHL patients, 48 had a T-cell type lymphoma, accounting for 17.6% of all NHL patients. Anaplastic large cell lymphoma was included in this group in accordance with the WHO classification. There were 14 patients with the latter type of lymphoma, 9 with the null-cell phenotype, and 5 expressing a T-cell phenotype. Of the remaining T-cell lymphomas, lymphoblastic T-cell lymphoma was the commonest (11 cases) followed by mycosis fungoides (10 cases), peripheral T-cell lymphoma (4 cases), angioimmunoblastic-like T-cell lymphoma (3 cases) and extranodal NK/T nasal type T-cell lymphoma (3 cases). There were 2 cases of enteropathy-associated T-cell lymphomas complicating coeliac disease, and 1 rare case of a primary splenic T-cell lymphoma of the gamma/delta phenotype (confirmed at the Mayo Clinic, Rochester, Minnesota, USA).

Table 1. Distribution of 272 patients with NHL according to the WHO classification

NHL type	No of cases (no. of extranodal cases)	Mean age (± 1 SD)	Gender (M/F)	No. with marrow involvement	% with marrow Involvement
B-cell lymphomas					
Precursor lymphoblastic	10 (4)	12.3 (7.3)	7/3	8	37.3
Small lymphocytic	10	64.1 (6.6)	8/2	9	67
Lymphoplasmacytic	4	64.8 (7.3)	3/1	4	75
Splenic marginal zone	1 (1)	40	1/0	1	0
Extranodal marginal (Malt type)	9 (9)	48.8 (12)	6/3	5	0
Nodal marginal	4	45.8 (7.9)	2/2	4	25
Follicular	54 (7)	56.8 (12.6)	28/26	45	58
Mantle cell	17 (2)	58.5 (12.5)	13/4	13	62
Diffuse large cell B-cell	98 (40)	46.3 (19.5)	58/40	43	19
Burkitt's	17 (15)	8.4 (6.6)	11/6	13	7.7
T-cell lymphomas					
Precursor lymphoblastic	11	19.2 (12.3)	6/5	9	33
Peripheral t-cell	4 (3)	37 (15)	1/3	4	50
Angioimmunoblastic	3	59 (5.3)	1/2	2	50
Extranodal NK/T-cell, nasal type	3 (3)	32.3 (4)	2/1	2	0
Enteropathy-type t-cell	2 (2)	38 (2.8)	2/0	2	0
Mycosis fungoides	10 (10)	48.5 (21.7)	7/3	5	0
Anaplastic large cell	14 (2)	37.1 (20.1)	8/6	11	18
Hepatosplenic g/d	1 (1)	18	1/0	1	100
Total	272 (99)	44.7 (21.3)	165/107	142	44.4

Trephine biopsy material from a unilateral site was available for 142 patients diagnosed as having NHL. Of the 142 cases that were examined, lymphoplasmacytoid lymphoma was the commonest NHL to have marrow involvement followed by small lymphocytic lymphoma, mantle cell lymphoma, and follicular lymphoma, in descending order. Among the follicular lymphomas, grade 1 follicular lymphomas had the highest incidence of marrow involvement with 9 of 10 cases (90%), followed by grade 2 with 12 of 20 cases (60%); only 4 of the 14 cases (28.5%) belonged to grade 3 follicular lymphomas. The latter is closer to the incidence of marrow involvement among patients with diffuse large B-cell lymphoma (21%).

Hodgkin's lymphoma Among the 75 patients diagnosed with HL, 40 patients were males (53.3%) and 35 were females (46.7%) with ages ranging from 3 to 64 years. There were 68 primary nodal cases, and 7 extranodal cases (4 splenic, 2 lung, 1 large bowel) that were confirmed after exclusion of other primary

sites by imaging studies. The most frequent nodal location was the cervical group of nodes (37 cases, 49.3%), followed by the anterior mediastinal nodes (13 cases, 17.3%), the axillary nodes (7 cases, 9.3%), and the inguinal and abdominal nodes (4 cases, 5.3%) each (Table 2). Of the 75 cases of HL, nodular sclerosis variant (NS) was the commonest subtype (27 cases, 36%). Of the latter, 20 were of grade 1 and 7 were of grade 2 subvariant. Mixed cellularity HL was the second most frequent (19 cases, 25.3%), followed by the lymphocytic predominant subtype (5 cases, 6.7%), the lymphocytic rich classic subtype (4 cases, 5.3%), and the lymphocytic depleted subtype (2 cases, 2.7%). There were 18 cases of classic HL (18%), which could not be further subtyped due to the small nature of the specimens.

At the initial presentation, 49 of the 75 HL patients had available bone marrow trephine biopsy from a unilateral site only. Among these patients, 6 (8%) had involved bone marrows (3 mixed, 2 classic, and 1 lymphocytic depleted).

Childhood lymphomas Of the 347 lymphoma patients, 49 were children aged <15 years (Table 3) accounting for 13% of all lymphoma cases during this 3-year study. In this age group, the commonest lymphomas were non-Hodgkin's B-cell lymphomas of Burkitt's type (15 cases) HL (14 cases) and lymphoblastic lymphoma (11 cases, 6 of B-cell and 5 of T-cell phenotypes). Among the Burkitt's group of patients, 13 had primary extranodal disease and 2 patients had nodal disease. There were 6 cases of diffuse large B-cell lymphoma, 2 cases of anaplastic large cell lymphoma (1 of T-cell and 1 of null-cell phenotype) and 1 rare case of mycosis fungoides presenting in a 13-year-old boy.

Extranodal lymphoma There were 106 cases of extranodal lymphomas accounting for 30.5% of all lymphomas (Table 4). The commonest site involved was the stomach with 21 cases, 12 of which were diffuse large B-cell lymphomas and 9 were low-grade lymphoma of the MALT type. The second most frequent affected site was the skin, with 17 reported cases.

Discussion

The spectrum of lymphomas in the Middle East is now emerging with several recently published reports that address this issue from our region.¹⁰⁻²⁰ The relative incidence of the pathologic subtypes of malignant lymphoma documented in our study is well representative of the population of Jordan, since this hospital-based study is a collective study of patients from all geographic regions in the country.

The classification of lymphomas has changed over the years, and currently most centres are adopting the WHO classification,² which incorporates the REAL classification¹ with minor modifications. This classification has proved to have a very good interobserver and intraobserver reproducibility in the diagnosis.

The results of our study showed a predominance of NHL (78.4%) compared with HL (21.6%) among the Jordanian population. These percentages are somewhat intermediate between studies done on Caucasians in the West, where the incidence of HL

Table 2. Distribution of 75 patients with HL according to WHO classification

HL Type	No of cases (No. of extranodal cases)	Mean age (± 1 SD)	Gender (M/F)	No. with Marrow involvement	% with marrow involvement
Lymphocytic predominant	5	22.6 (4.7)	3/2	5	0
Lymphocytic rich classic	4	31.3 (20.5)	3/1	4	0
Mixed cellularity	19 (1)	31.3 (17.5)	12/7	8	37
Nodular sclerosis					
grade 1	20 (4)	27.9 (14.5)	7/13	9	0
grade 2	7 (1)	33.1 (20.7)	4/3	6	0
Lymphocytic depleted	2	49 (15.6)	1/1	2	50
Classic HL (NOS)	18 (1)	34.2 (17.7)	10/8	15	13
Total	75 (7)	31.1 (16.6)	40/35	49	12

Table 3. Distribution of 49 cases of various childhood lymphomas.

Type of Lymphoma	No. of cases	Mean age (± 1 SD)	Gender M/F	No. with Marrow involvement	% with marrow involvement
Burkitt's	15	6.4 (2.9)	11/4	12	8.3
Hodgkin	14	9.9 (4.3)	6/8	7	0
Lymphoblastic	11	7.3 (3.4)	7/4	11	18.2
Diffuse large B-cell	6	8.7 (3.7)	5/1	3	0
Anaplastic	2	12.5 (0.7)	1/1	2	0
Mycosis fungoides	1	13	1/0	1	0
Total	49	8.2 (3.7)	31/18	36	8.3

Table 4. Extranodal presentations of 106 lymphoma cases.

Site of lymphoma	No. of cases
Stomach	21
Skin	17
Small and large bowel	12
Spleen	11
Pharyngeal tonsils	11
Bone	8
Nasal cavity and nasopharynx	6
Soft tissue	6
Lung	5
Thyroid	3
Adrenal	2
Parotid gland	2
Ovary	1
Brain	1

ranges from 25% to 40%, and percentages from studies on Orientals in the Far East, where the incidence of HL ranges between 5% to 10%.²¹ In comparison with other studies from the Middle East, namely those from Saudi Arabia, Oman, Bahrain and the UAE,¹⁰⁻¹⁵ this study shows both similarities and differences in certain areas. The incidence of HL is comparatively more frequent, with figures of 27% in Saudi Arabia, 35% in Oman, 33% in Bahrain, and 41% in the UAE reported in the literature. Among the various subtypes of HL, the nodular sclerosis variant was found to be the commonest subtype in our study (47.4%) followed by the mixed cellularity variant (33%). This result differs from another study in Jordan²⁰ in which mixed cellularity HL was slightly commoner than nodular sclerosis variant. These differences might be explained by geographical differences as our study represents patients from all regions of the country in contrast to their study, which looked at patients from one region in the north of Jordan. The results of this study however are similar to results from other countries in the region such as Kuwait,¹³ UAE,¹⁰ and Saudi Arabia.^{14,15} In one study from Saudi Arabia,¹⁵ a change in trend has recently been noticed, with nodular sclerosis HL becoming the commonest variant. The higher values for the mixed cellularity subtype in Oman¹² and Bahrain¹¹ are in contrast to our study, but the number of patients in these studies was noticeably less than in ours. No important difference was found in the percentage of various subtypes of HL from those in the West^{22,23} where nodular sclerosis is reported to be the commonest variant.

With regards to specific subtypes of NHL, this study showed that diffuse large B-cell lymphoma is the most commonly encountered lymphoma, accounting for 28.2% of all cases. This particular lymphoma is also reported to be the commonest subtype from all studies carried out in the region of the Middle East and is similar to studies from North America, Europe and several countries in the Far East such as Japan and Thailand.³⁻¹⁵ Compared with other countries in the Middle East, there appears to be a higher incidence of low grade NHL of the B-cell type among the Jordanian people, which

accounts for 24% of all lymphoma cases when using the working formulation, which is similar to studies in North America and Europe (26-46%),²⁴ but is significantly higher than some studies in our region such as in the UAE and Saudi Arabia (<10%).^{10,14}

In Jordan, T-cell lymphomas are uncommon, representing 17.6% of all NHL cases. The percentages of these lymphomas are slightly higher than in other regional countries where the incidence of T-cell lymphomas have varied between 7% to 13%, but is significantly less than reports from the majority of countries in Asia where an incidence of these lymphomas ranging between 16% and 40% have been documented.⁶⁻⁹

Our study describes the pattern of lymphoma in the paediatric group of patients (age <15). In this age group, Burkitt's lymphoma and HL are the commonest types followed closely by lymphoblastic lymphoma. Burkitt's lymphoma was encountered in most cases at extranodal sites and in particular in the ileocaecal region, followed by a primary bone origin, namely the jaw and pelvis. The second most frequent lymphoma in this group was HL. These findings are significant since both of these lymphomas have been shown to have an etiologic association with Epstein-Barr virus.

Extranodal lymphomas (ENL) are common. In our study they accounted for 30.5% of all lymphomas and 36.4% of all NHL cases, with the gastrointestinal tract being the most commonly affected site. These figures are close to the incidence of ENL in other countries in the region, such as the UAE (29%) and Bahrain (41%).^{10,11} The incidence of these lymphomas in this region of the Middle East is slightly higher than in the USA (26%),²⁴ but is less prevalent than in some Asian countries such as China and Korea where the incidence of ENL has comprised more than half of all lymphomas.^{8,9,23} In our study the incidence of bone marrow involvement at the initial presentation was high for low grade B-cell lymphomas (55-75%) compared with high-grade lymphomas such as diffuse large B-cell lymphoma (19%). Interestingly, grade 3 follicular B-cell lymphoma was found to have a percentage marrow involvement (28%) closer to that of diffuse large B-cell lymphoma in contrast to the percentage involvement in grade 1 and 2 follicular lymphoma (90% and 60%, respectively). In both adults and children, Burkitt's lymphoma had a low incidence of marrow involvement (7.7% and 8.3%, respectively). There was a low incidence of marrow involvement at the initial presentation of patients with HL.

In conclusion, this is one of the few large-scale studies conducted in Jordan on the pattern of lymphomas using immunohistochemical markers. The use of the current WHO classification of lymphoid neoplasm helps to unify the terminology of the various subtypes

of lymphomas for future comparative studies across the region. In Jordan the most common lymphoma is the diffuse high grade B-cell lymphoma, but the commonest lymphomas in the paediatric group of patients are Burkitt's and Hodgkin's lymphomas.

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