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Classification of non-Hodgkin lymphoma in the Middle Euphrates Region of Iraq according to the World Health Organization classification

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Abstract:

BACKGROUND: Non-Hodgkin lymphoma (NHL) patterns vary worldwide in relation to demographic and environmental factors.

AIM: The objective of our study was to identify subtypes of NHL in the Middle Euphrates Region of Iraq according to the World Health Organization (WHO) modified classification.

MATERIALS AND METHODS: A retrospective descriptive study was carried out at Al-Hussein Cancer Center in Karbala, Iraq, on 385 patients diagnosed with NHL between January 2012 and August 2020. Patient ages ranged between 1 and 96 years. They included 204 males and 181 females. All patients were diagnosed by tissue biopsy, confirmed by immunohistochemistry markers, and classified according to WHO classification. Any patient with inconclusive results was excluded from the study.

RESULTS: Among total NHL patients, males were (53%) and females were (47%) with a male: female ratio of (1.12:1). B-cell lymphoma was diagnosed in (92.47%) and T cell lymphoma in (7.53%). Diffuse large B-cell Lymphoma (DLBCL) was the most frequent B-cell subtype (54.02%) followed by Burkitt's lymphoma (BL) (14.02%), while peripheral T-cell lymphoma was the most common T-cell subtype (2.08%). About (61.82%) of patients were nodal, and (38.18%) were extranodal. The intestine was the most frequent extranodal site (34.69%).

CONCLUSION: Among our patients, there were high frequencies of DLBCL, extra nodal primaries and intestinal BL. Follicular lymphoma and small lymphocytic lymphoma were uncommon in our region. These results were similar to the Middle Eastern NHL patterns but differed from the western patterns.

Keywords:

Iraq, non-Hodgkin's lymphoma, World Health Organization classification

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Introduction

Non-Hodgkin's lymphoma (NHL) is a group of lymphoproliferative neoplastic disorders of nonhomogenous histological and clinical pattern. It is the 7th most common tumor reported in the United States.^[1,2] Its occurrence has steadily increased over the last few decades.^[3]

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Lymphoma is commonly originated in lymph nodes; the most frequent sites are cervical, inguinal, and axillary lymph nodes. Invasion of malignant lymphocytes in organs other than lymph nodes is called extranodal lymphoma; therefore, any organ inside the body can be affected. [4,5]

The classification of lymphoma is complex and has changed throughout the years. There are many subtypes within each type of NHL depending on how quickly the

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tumor grows (aggressive or indolent) and on the type of lymphocytes involved (B-cells, T-cells, or natural killer cells [NK]). Over the recent years, lymphoma classification has improved, and that is reflected in the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. [6] It identifies over forty mature B-cell neoplasms and over 25 mature T-cell and NK cell neoplasms. [7] Various NHL subtypes differ greatly between various geographical locations around the world. Moreover, lifestyle and environmental factors play a critical role in the development of NHL. [8]

In a previous study carried out in northern Iraq, most NHLs were of B-cell type, and the highest percentage was of diffuse large cell type. ^[9] In Southern Iraq, it was reported that lymphomas were more frequent in men, NHL was more common than Hodgkin lymphoma (HL), one HL case was diagnosed for every three NHL cases, and diffuse large B-cell lymphoma (DLBCL) was the most common subtype of NHL. ^[10]

The objective of our study was to identify subtypes of NHL in the Middle Euphrates Region of Iraq according to the WHO modified classification.

Materials and Methods

Study design and participants

This is a retrospective descriptive study conducted at Al-Hussein Cancer Center in Karbala, Iraq. The patients registered from different governorates including Najaf, Babylon, Al-Qadisiyah, and Al-Muthanna. It covers not only Karbala area, but other patients from the Middle Euphrates Region in Iraq are referred to this center for solid and hematological malignancy management. The study included 385 NHL patients diagnosed with NHL between January 2012 and August 2020. Patient ages ranged between 1 and 96 years, the median age was 50 years, they included 204 males and 181 females [Table 1 and Figure 1]. All patients were diagnosed according to the 2016 revision WHO

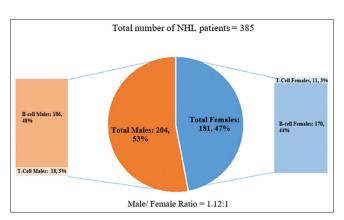


Figure 1: Distribution of males and females

classification of lymphoid neoplasms by tissue biopsy and confirmed by immunohistochemistry (IHC) markers. [6] IHC panel used for lymphoma was BCL6, BCL2, CD79a, CD30, CD23, CD20, CD15, CD10, CD8, CD5, CD4, CD3, anaplastic lymphoma kinase-1, terminal deoxynucleotidyl transferase, Ki67 and Cyclin D1. The biopsies were reviewed by two expert pathologist in pathology department before final diagnosis.

Inclusion/exclusion criteria

Included in this study were patients diagnosed with NHL between January 2012 and August 2020, diagnosed by excisional biopsy and IHC and classified according to the WHO classification. Any patient with inconclusive results diagnosed with fine-needle aspiration or core biopsy were excluded from this study.

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Karbala Teaching Hospital in Karbala, Iraq.

Statistical analysis

Data of all patients were entered and managed using the Statistical Package for Social Sciences software (SPSS 25, IBM, Armnok, NY, United State Of America). Descriptive statistics of the variables were expressed as percentage, median, and ratio.

Results

Figure 1 presents the distribution of males and females among our sample. There were 385 patients with NHL enrolled in our study. They included 204 males (53%) and 181 females (47%) with a male: female ratio (1.12:1).

Table 2 presents the distribution of NHL histological subtypes by median age, gender, and extranodal involvement. The most frequent lymphoma was B-cell lymphoma in 356 patients (92.47%) and T-cell lymphoma in 29 patients (7.53%). Regarding B-cell lymphoma subtypes, the most common histological subtype was DLBCL diagnosed in 208 patients (54.02%) followed by Burkitt's lymphoma (BL) in 54 patients (14.02%),

Table 1: Age distribution of 385 patients

Age (year)	n (%)
≤10	58 (15.06)
11-20	22 (5.71)
21-30	18 (4.68)
31-40	41 (10.65)
41-50	65 (16.88)
51-60	69 (17.92)
61-70	66 (17.14)
71-80	35 (9.09)
>80	11 (2.86)
Total	385

mucosa-associated lymphoid tissue (MALT) lymphoma in 25 patients (6.49%), small lymphocytic lymphoma (SLL) in 18 patients (4.67%), nodal marginal zone lymphoma in 15 patients (3.90%), follicular lymphoma (FL) in 13 patients (3.38%), lymphoplasmacytic lymphoma in 12 patients (3.12%), mantle cell lymphoma in 6 patients (1.56%), splenic marginal zone lymphoma in 4 patients (1.04%), and mediastinal large B-cell lymphoma in 1 patient (0.26%). Regarding T-cell lymphoma subtypes, the most common histological subtype was peripheral T-cell lymphoma (not otherwise specified) in 8 patients (2.08%) followed by anaplastic large T-cell lymphoma in 5 patients (1.30%), angioimmunoblastic T-cell lymphoma and precursor T-lymphoblastic lymphoma/leukemia in 4 patients (1.04%) each, extranodal NK/T-cell lymphoma nasal type, cutaneous anaplastic large cell lymphoma, and mycosis fungoides in 2 patients (0.52%) each, aggressive NK-cell leukemia and enteropathy associated T-cell lymphoma in 1 patient (0.26%) each.

Figure 2 presents the distribution of nodal and extranodal NHL patients. In our study, 238 patients (61.82%) had nodal primaries. Primary extranodal NHL had been observed in 147 cases (38.18%).

Table 3 presents the extranodal sites of NHL according to the primary origin. The intestine was the most commonly affected site of extranodal NHL in 51 patients (34.69%), BLs and DLBCL constituted the bulk of primaries involving the intestine. Stomach was the second most affected site in 19 patients (12.93%), followed by tonsils in 14 patients (9.52%), bones, and nasopharynx in 7 patients (4.76%) each, thyroid and skin in 6 patients (4.08%) each, testis in 5 patients (3.40%), bone marrow in 4 patients (2.72%), thigh, breast, and maxillary sinus mass in 3 patients (2.04%) each, and other site involvement details which are presented in the table.

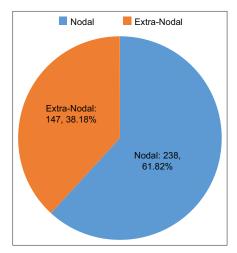


Figure 2: Distribution of nodal and extra-nodal non-Hodgkin lymphoma

Discussion

NHL is a group of lymphoproliferative neoplastic disorders with multiple clinical and biological features. It has a significant geographic variation among histological subtypes. [8,12] In the Middle Euphrates Region of Iraq, lymphoma represents the second most common malignancy just after breast cancer. [11]

To the best of our knowledge, this is the first statistical study to identify the different subtypes of NHL in Middle Euphrates Region. It can help to provide basic information, assess the progress in recent years, and to develop future lymphoma treatment strategies in this area of our county.

There was a male predominance in our sample with a male: female ratio of (1.12:1) which is similar to what was reported by other studies in North Iraq, [13] Greece, [14] India, [15] and Saudi Arabia. [16] The median age was 50 years, close to Egypt, [17] but relatively older than what was reported in Pakistan (45 years), [18] Turkey (43 years), [19] and Jordan (44 years). [20] On the other hand, our reported median age was younger than that reported in the United States (67 years) [21] and the United Kingdom (69 years).

Our results revealed that the B-cell subtype represented (92.47%) of all NHL while the T-cell subtype represented only (7.53%). This result was comparable to other studies in the North of Iraq,^[23] Jordan,^[20] and Greece.^[14] However, in other studies, the reported B-cell NHL percentages were much lower in India (66%),^[15] China (64.7%),^[24] Japan (75%),^[25] and Korea (77.6%).^[26] This variation between developing and developed countries may be due to better diagnostic criteria of T-cells lymphoma and a wide panel of IHC that available in developed countries.

In our study, DLBCL was the most common subtype of NHL, counting for (54.02%) of all NHL, which was similar to studies reported in Saudi Arabia (59%),^[16] Jordan(53%),^[20] and Kuwait (58.6%).^[27] While, it was higher than that reported in Pakistan (30.9%),^[18] Turkey (41%),^[19] China (40.9%),^[24] and Korea (42.7%).^[26] Genetics, racial, and environmental factors may be responsible for the disparities.

BL was the second most frequent NHL in our study (14.02%) with a median age of 6 years. It was the most frequent NHL in children as they represent more than 15% of collected sample. This was similar to North Iraq (14.6%) with a median age of (6 years)^[23] and Jordan (14.41%) with a median age of (4.5 years).^[20] A lower percentage was reported in India^[15] and Kuwait^[27] which accounted for (6%) of all NHL. On the other hand,

Table 2: Distribution of non-Hodgkin lymphoma histological subtypes by median age, gender, and extranodal involvement

NHL types	n (%)	Median	Gender		Extranodal
		age (years)	Males	Females	involvement
B-cell					
DLBCL	208 (54.02)	51	94	114	59
BL	54 (14.02)	6	36	18	51
MALT-lymphoma	25 (6.49)	58	15	10	25
Small lymphocytic lymphoma	18 (4.67)	57	8	10	0
Nodal marginal zone lymphoma	15 (3.90)	58	6	9	0
Follicular lymphoma	13 (3.38)	56	7	6	1
Lymphoplasmacytic lymphoma	12 (3.12)	14	12	0	2
Mantle cell lymphoma	6 (1.56)	71	4	2	1
Splenic marginal zone lymphoma	4 (1.04)	64	3	1	0
Mediastinal large B-cell lymphoma	1 (0.26)	62	1	0	0
Total	356 (92.47)		186	170	139
T-cell					
Peripheral T-cell lymphoma (NOS)	8 (2.08)	45	5	3	0
Anaplastic large T-cell lymphoma	5 (1.30)	47	2	3	0
Angioimmunoblastic T-cell lymphoma	4 (1.04)	55	3	1	0
Precursor T-lymphoplasticlymphoma	4 (1.04)	42	3	1	1
Extranodal NK/T-cell lymphoma, nasal type	2 (0.52)	54	1	1	2
Cutaneous anaplastic large cell lymphoma	2 (0.52)	46	1	1	2
Mycosis fungoides	2 (0.52)	51	2	0	2
Aggressive NK-cell leukemia	1 (0.26)	62	0	1	0
Enteropathy associated T-cell lymphoma	1 (0.26)	40	1	0	1
Total B cell	29 (7.53)		18	11	8

DLBCL=Diffuse large B-cell Lymphoma, MALT=Mucosa-associated lymphoid tissue, NOS=Not otherwise specified, NK=Natural killer cells, NHL=Non-Hodgkin lymphoma, BL=Burkitt's lymphoma

BL reported the lowest incidence in Greece (1.9%),^[14] UK (2.17%),^[22] China (1.1%),^[24] and Egypt (<1%).^[17] The high incidence in Middle East countries may be explained by the exposure to Epstein-Barr virus (EBV) infection in this part of the world.

The current study showed that MALT lymphoma accounted for (6.49%) among total NHL, which was reported as the third frequent subtype. Similar results have been reported in Japan (6.3%),^[25] Taiwan (7.71%),^[12] and the United States (8.3%).^[21] However, it was higher than that reported in Jordan (3.6%)^[20] but lower than that reported in Greece (10.4%)^[14] and the United Kingdom (19.81%).^[22]

Our results showed that SLL accounted only to (4.67%) of all NHL, which was much lower than that reported in the United States (18.6%) where it was the second common NHL. [21] In Jordan and China, SLL percentage was lower than that reported in our study ([1.8%] and [3.2%] respectively). [20,24] While SLL reported slightly higher percentages in Taiwan (6.04%) [12] and Greece (6.4%). [14] Our finding may be explained by that SLL is a disease of the old age population and only (3.4%) of the Iraqi population are above 65 years. [28] Furthermore, most patients with SLL are asymptomatic, and they did not need treatment leading to under registration. On the

other hand, some of SLL patients may misdiagnosed as chronic lymphocytic leukemia in our region.

In our study, FL showed a low rate (3.38%) of all NHL, and this was similar to a study reporting (2.9%) in the north of Iraq, while FL in other countries reported higher percentages compared to that reported in our study such as Japan (19.3%), think is united States (17.1%), think is united States (17.1%), think is revealed that (FL) remained the lowest in developing Asian countries, may be as results of regional genetic or environmental factors that contributed to such pattern. However, the epidemiology pattern is likely to change with improved living conditions, longer life expectancy, westernized living habits, and the HIV epidemic. [29]

Our study showed that the most frequent subtype of T-cell NHL was peripheral T-cell lymphoma, similar to what was reported in the United States,^[21] Japan,^[25] Greece,^[14] and Jordan.^[20] On the other hand, other studies reported that the most frequent subtype of T-cell NHL was anaplastic large T-cell lymphoma such as in north Iraq^[13] and India.^[15] While in China, extranodal NK/T-cell lymphoma nasal type was the most frequent subtype.^[24] These differences may be explained by the fact that the prevalence of the EBV, which is the major

Table 3: Extranodal site of non-Hodgkin lymphoma according to primary origin

Sites	n (%)
Intestinal	51 (34.69)
Stomach	19 (12.93)
Tonsil	14 (9.52)
Bone (mandible, sternal, spines, sacral and tibia)	7 (4.76)
Nasopharynx	7 (4.76)
Thyroid	6 (4.08)
Skin	6 (4.08)
Testis	5 (3.40)
Bone marrow	4 (2.72)
Thigh mass	3 (2.04)
Breast	3 (2.04)
Maxillary sinus mass	3 (2.04)
Pleural mass	2 (1.36)
Pancreas	2 (1.36)
Lung mass	2 (1.36)
CNS	2 (1.36)
Adrenal	2 (1.36)
Liver	2 (1.36)
Oropharyngeal mass	2 (1.36)
Renal	1 (0.68)
Ovarian mass	1 (0.68)
Larynx	1 (0.68)
Orbital mass	1 (0.68)
Para-spinal mass	1 (0.68)
Total	147 (100)

CNS=Central nervous system

contributing factor related to NK/T-cell lymphoma, is different between regions even within the Asian countries. [29,30]

Extranodal NHL in this study accounted for (38.18%) of the total cases. This result was lower than to what was reported in other studies in Kuwait (45%),^[27] Turkey (44.5%),^[19] India (43%),^[15] Jordan (43%),^[20] Korea (69.9%),^[26] and Iran (42%).^[31] In Greece, the extranodal involvement accounted for (31.6%),^[14] which was lower than that reported in our study. In recent years, increments in diagnosis of extranodal are explained by the improvement in diagnostic methods such as IHC, and flow cytometry, which have greatly enhanced the diagnosis and its confirmation for lymphoma and hematological malignancies.^[32]

In our study, the gastrointestinal tract seemed to be the most common site of involvement, and the intestine was the most commonly affected organ. These results were similar to what was reported in north Iraq, [23] Turkey, [19] and Jordan. [20] While in other countries such as Saudi Arabia, [16] China, [24] and Korea, [26] the stomach was the most common site. This may be due to Immunoproliferative small intestinal disease is prevalent in our region with late presentation that already transforming lymphoma at diagnosis. [33]

Our study can be evaluated in terms of its strengths and limitations. A strength of our study is that it can help to provide basic information about NHL in Iraq, comparing it to neighboring countries and the world. Moreover, to the best of our knowledge, this study is the first one to be carried out in the Middle Euphrates Region. A limitation of our study is that it covered only the Middle Euphrates Region and not other regions of Iraq.

Conclusion

In our study, B-cell lymphoma represented the majority of cases. DLBCL was the most frequent B-cell subtype, while peripheral T-cell lymphoma was the most common T-cell subtype. Interestingly, childhood BL was the second most common lymphoma in our region. Extranodal NHL was common among Iraqi patients, and unlike western studies, the intestine was the most affected site. This unique pattern of NHL in the Middle Euphrates Region highlights the need for future studies in other parts of Iraq with a larger number of patients to understand the lymphoma dissemination and pattern in this country.

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Conflicts of interest

There are no conflicts of interest.

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