

A STUDY OF LYMPHOMAS IN SELECTED CENTERS IN TEHRAN, BASED ON THE UPDATED KIEL CLASSIFICATION

Mohammad Hashemi MD*, Mohammad-Reza Parwaresh MD**

**Department of Pathology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ** Institute of Hematopathology, Christian Albrechts University, Kiel, Germany*

Abstract

Objective-The present study aims at examining the lymphomas in Iran and the similarities and differences with those of western countries.

Methods-In a descriptive observational study, the histochemical and immunohistochemical markers were used to examine the biopsied specimens of 263 patients with Hodgkin's and non-Hodgkin's lymphomas collected from six diagnostic centers. The non-Hodgkin's and Hodgkin's lymphomas were classified according to the updated Kiel classification and Rye classification, respectively.

Results-Out of the 225 cases that were diagnosed as lymphomas, 170 were non-Hodgkin's and 55 were Hodgkin's lymphomas. Sixty-nine percent of the Non-Hodgkin's lymphomas were of the B-type, 6.5 percent of the T-type and the rest were Hodgkin's lymphomas (24.5 %).

Conclusion-The comparison made between the findings of this study and those of western countries indicates that high-grade non-Hodgkin's lymphomas are more prevalent than low-grade lymphomas in Iran. The use of the updated Kiel classification reveals the similarities and differences between the lymphomas of our study and those of western studies. Such studies provide useful information for a more precise diagnosis and hence more success in the treatment of lymphomas. The results also call for more research into the reasons for the prevalence of high-grade lymphomas and rare occurrence of follicular lymphomas in Iran.

Keywords • Hodgkin's lymphoma • non-Hodgkin's lymphoma • updated Kiel classification • immunohistochemistry

Introduction

A high occurrence of malignant lymphomas, 8.4% of all cancers, has been reported in studies conducted in Iran.¹ While further research in this area is necessary for a better understanding of the reasons underlying this finding, a sound and acceptable classification is needed for the better comparison of such studies. Classifying various types of lymphomas is not an easy task as there are seven classification systems and one working formulation in use at present.² In this study,

malignant lymphomas were classified using the updated Kiel classification which is based on cytomorphology, immunophenotype and cellular differentiation³ while other classifications, such as Rappaport's are based purely on cytomorphology and lack comprehensiveness. Another advantage of adopting the Kiel classification is that the use of a common classification results in a better understanding of the similarities and differences of the results. This allows for the comparability of the results of our study with those of western countries, which have used similar classification systems.

Two similar studies have been conducted in Iran by Tabei, et al and Tabrizchi, et al.^{4,5} In the first study, conducted at Shiraz University, 294

•Correspondence: M. Hashemi MD, Imam Hossein Hospital, 16179 Tehran, Iran, Fax: +98-21-7557069 E-mail: M.Hashemi@morva.net.

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cases of lymphomas from Fars and Khorasan provinces were classified according to the working formulation using hematoxylin and eosin staining solely. In addition to not relying on immunohistochemistry and histochemical stains, they did not differentiate the distribution of Non-Hodgkin's lymphomas of T-cells and B-cells types. Tabrizchi, et al investigated 162 cases from the cities of Kerman and Tehran using new methods of immunohistochemistry and histochemistry based on the Kiel classification. However, since there were only 91 cases of non-Hodgkin's lymphomas the results may not be considered as conclusive.

Compared to the above-mentioned studies, the present study has investigated a larger sample, with more monoclonal antibodies and has adopted the updated Kiel classification method.

Patients and Methods

In the present study, 225 cases of malignant lymphomas (various types of Hodgkin's and non-Hodgkin's lymphomas), collected from six diagnostic centers from Tehran, (Taleghani Hospital, Imam Hossein Hospital, Loghman Hakim Hospital, Boo-Ali Hospital, and two private diagnostic centers; Armin Laboratory and Bank Melli Hospital) were investigated. Relevant clinical data, including age, gender and the site of specimen sampling, were recorded.

The primary diagnosis was based on formalin fixed paraffin sections of three-micron thick slices, stained with H&E, periodic acid schiff (PAS), Giemsa and silver. In cases where histochemical methods did not yield conclusive results, the differentiation of Hodgkin's lymphoma and non-Hodgkin's lymphoma, from epithelial, mesenchymal and myeloproliferative lesions, were made using immunohistochemical methods with the following markers (6):

K11, PanLeuc(CLA)L26, CD3, UchL1, β F1, K, λ ,

μ , Kis5, CD30, LMP, KiM1P, KiM4p, KiMy2, KiMy1, KiB5, A10, BcL2, S100.

Non-Hodgkin's lymphomas were marked based on the Kiel classification and Hodgkin's lymphomas on the Rye classification.⁷

The frequency of occurrence of the lymphomas according to age, gender and site of involvement were also noted.

Results

Two-hundred and twenty-five cases out of 263 were malignant lymphomas of which 170 and 55 were non-Hodgkin's and Hodgkin's lymphomas, respectively. The remaining cases (n=38), which were not lymphomas, were as follows:

1. The samples taken from 21 cases were of poor quality and unrecognizable, inadequate for diagnostic purposes or were not from lymphatic tissues.
2. Eight cases were diagnosed as metastatic carcinoma of which 2 were nasopharyngeal anaplastic carcinoma, 2 were oat cell carcinoma, 3 were of unknown origin metastatic carcinoma and one was a case of gastric adenocarcinoma.
3. Five cases revealed a hyperimmune reaction and chronic non-specific lymphadenitis.
4. Three cases were diagnosed as AML (M2, M5a).
5. One other case was diagnosed as embryonal rhabdomyosarcoma.

The distribution of B-cell and T-cell non-Hodgkin's lymphomas and Hodgkin's lymphomas, according to age and gender is shown in Table 1. As indicated in Table 1, 155 cases (91.2%) are of the B-type and 15 cases (8.8%) are of the T-type. Table 2 indicates grading, age, gender and site of involvement in B-cell lymphomas. Table 3 shows the distribution of non-Hodgkin's T-cell and B-cell lymphomas and Table 4 indicates the distribution

Table 1. Distribution of lymphomas according to gender and age.

Type of lymphoma	No. of cases	Percentage	Ratio of M/F	Mean age (range)
Hodgkin's lymphoma	55	24.5	1.6:1	34 (6-70)
Non-Hodgkin's lymphoma, B-cell type	155	69	1.7:1	46.7 (1-90)
Non-Hodgkin's lymphoma, T-cell type	15	6.5	12:1	40 (20-72)
Total	225	100	5:1	40 (1-90)

Table 2. Distribution of B-cell non-Hodgkin's lymphoma according to gender, age and main sites of involvement.

Subclass of malignant lymphoma	No. of cases	Percentage	Ratio of M/F	Mean age (range)	Main site of involvement
Low-grade malignant lymphoma	34	22	1.7:1	52 (25-89)	Cervical nodes (8)
Lymphocytic CLL PLL HCL	6	4	2:1	63 (47-80)	Cervical nodes (2)
Immunocytoma	12	8	2:1	53 (25-75)	Cervical nodes (5)
Plasmocytic	4	2.5	3:1	54 (44-69)	Vertebra (2)
Centroblastic/centrocytic (cb/cc)	3	2	1:2	45.5 (42-47)	Axillary nodes (1)
Centrocytic (mantle cell lymphoma)	2	1.3	2:0	50	Cervical nodes (1)
Monocytoid B-cell lymphoma	2	1.3	1:1	44 (32-56)	Mesenteric nodes (2)
Malt (special type=clc) lymphoma*	2	1.3	2:0	41.5 (30-53)	Small (1) & large bowel (1)
Malt (immunocytoma type) lymphoma*	1	0.6	0:1	53	Orbit (1)
IPSID*	2	1.3	1:1	64	Small bowel (1) & stomach (1)
High grade malignant lymphoma	121	78	1.7:1	41.5 (1-90)	Neck (35)
Centroblastic	77	50	2:1	45 (1-90)	Neck (31)
Immunoblastic	7	3.5	5:1	50 (29-70)	Axillary (2) & cervical nodes (2)
Burkitt's lymphoma	25	16	3:1	18 (4-72)	Abdomen (13)
Large cell anaplastic lymphoma (Ki-1)	1	0.6	1:0	52	Axillary nodes (1)
Lymphoblastic	5	3.2	1:4	24 (2-54)	Axillary nodes (1)
Rare type lymphomas:					
T-cell rich B-cell lymphoma	1	0.06	1:0	31	Axillary nodes (1)
High grade sclerosing B-cell lymphoma of mediastinum	3	2	1:2	43.5 (32-55)	Cervical nodes (2) Mediastinum (1)
Unclassified lymphoma	2	1.3	2:0	55 (52-58)	Bone marrow (2)
Total	155	100	1.7:1	46.7 (1-90)	Neck (43)

*These lymphomas which are extranodal are not mentioned in the Kiel classification.

of Hodgkin's lymphoma based on the Rye classification.

Discussion

Studies conducted in the Middle East and Iran indicate a high occurrence of lymphoma in the region. In the first published statistics in 1965, Habibi showed that 8.4% of all the cancers in Iran were malignant lymphoma. The results of Habibi's

study were later confirmed by Haghghi, et al in 1971 indicating that 7.6% of all cancers in southern Iran were malignant lymphomas.⁸

High percentage of malignant lymphoma is reported in studies conducted in countries of the Middle East such as 10.3% in Hejaz, Saudi Arabia, 13.5% in Iraq and 11.7% in Lebanon. In marked contrast, the findings of studies conducted in the United States by the American Cancer Society, and in Denmark by IARC indicate that the percentage

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Table 3. Distribution of T-cell and B-cell Hodgkin's lymphomas

Type of lymphoma			
B-cell	No. (%)	T-cell	No. (%)
Low-grade malignant lymphomas	34 (20%)	Low grade malignant lymphomas	1 (0.6%)
Lymphocytic		Lymphocytic	
CLL, PLL, HCL	6 (3.5%)	CLL, PLL	--- ---
		Small cell cerebriform	--- ---
Immunocytoma	12 (7%)	(mycosis fungoides and Sezary syndrome)	--- ---
Plasmocytic	4 (2.3%)	Lymphoepithelial lymphoma (LeL)	--- ---
Centroblastic-centrocytic (cb/cc)	3 (1.8%)	AILD (lgx) type	--- ---
Centrocytic (mantle cell lymphoma)	2 (1.2%)	T-zone lymphoma	--- ---
Monocytoid B-cell lymphoma	2 (1.2%)	Pleomorphic small cell	1 (0.6%)
Malt lym (special type-clc)*	2 (1.2%)		
Malt (immunocytoma type)*	1 (.6%)		
IPSID*	2 (1.2%)		
High-grade malignant lymphomas	121 (71.2%)	High-grade malignant lymphomas	14 (8.2%)
Centroblastic	77 (45.3%)	Pleomorphic medium sized and large cell	6 (3.5%)
Immunoblastic	7 (4.1%)	Immunoblastic	--- ---
Burkitt's lymphoma	25 (14.7%)		
Large cell anaplastic lymphoma (Ki-1)	1 (0.6%)	Large cell anaplastic lymphoma (Ki-1)	3 (1.8%)
Lymphoblastic	5 (2.9%)	Lymphoblastic	4 (2.3%)
Rare type lymphomas:			
T-cell rich B-cell lymphoma	1 (0.6%)		
High grade sclerosing B-cell lymphoma of mediastinum	3 (1.8%)		
Unclassified	2 (1.2%)	Unclassified	1 (0.6%)
Total	155 (91.2%)		15 (8.8%)

*The lymphomas, which are extranodal, are not mentioned in the Kiel classification

of malignant lymphomas, compared to other cancers, is 1.9% and 1.6% respectively.⁹ The high incidence of malignant lymphoma in Iran and the Middle East, compared to western countries, calls for further research in this area which remains relatively unexplored area.

In order to explore the similarities and differences between western countries and Iran, a comparison between the present study and those studies supervised by Lennert and registered with the

Lymph Node Registry in Kiel, Germany has been undertaken.

Table 5 is reproduced from Lennert and Feller study of 1992 and shows the distribution of 1284 cases of all types of non-Hodgkin's lymphomas in Germany.⁶

A comparison between Table 3 and Table 5 reveals the characteristics of non-Hodgkin's lymphomas as well as the overall similarities and differences between lymphomas in Iran and the

Table 4. Distribution of all types of Hodgkin's lymphoma according to gender and age

Subtype of Hodgkin's	No. of cases	percentage	M/F	Mean age (range)
Mixed cellularity	25	45.4	2:1	39 (8-70)
Nodular sclerosis	20	36.4	2:1	30 (6-66)
Lymphocytic depletion	3	5.4	1:1	36.5 (29-44)
Lymphocytic predominance	7	12.8	1.5:1	31 (18-57)
Total	55	100	1.6:1	34.5 (6-70)

West.

The results of this comparison are discussed in two sections. Section A is related to non-Hodgkin's lymphomas and section B is related to Hodgkin's lymphomas.

Section A

1. Non-Hodgkin's T-type lymphomas were 8.8% in the present study and 17.1% in the Kiel studies. Thus, there is a lower incidence of non-Hodgkin's T-type lymphomas in Iran compared to the West.
2. Considering the degree of malignancy, the majority of B-type lymphomas of the present study were high-grade lymphomas (72.2%) whereas with the Kiel studies, the majority of lymphomas were of the low-grade type (54.5%). One reason for this difference could be due to the low mean age of the population in Iran compared to western countries. Inadequate screening of patients might have also contributed to the difference. In addition, the patients often present themselves to the medical care system at much later stages of the disease where the low-grade lymphomas have evolved into secondary types of high-grade ones. For a more precise understanding of this phenomenon it is necessary to examine the etiology and the epidemiology of the lymphomas in Iran because there is the possibility that high-grade lymphomas in Iran are of the primary type and some important factors may be involved in higher occurrences.
3. In the present study, the most common low-grade B-cell lymphoma was immunocytoma with 12 cases (7%) and the most common high-grade B-cell lymphoma was centroblastic lymphoma with 77 cases (45.3%). However in the Kiel Lymph Node Registry the most common low-grade lymphoma was

centroblastic/centrocytic with 262 cases (accounting for 20.4%) and the most common high-grade lymphoma was centroblastic, with 176 cases (accounting for 13.7% of all cases). Thus, while there are similarities between the high-grade lymphomas, there seems to be a marked difference between the low-grade lymphomas. The cause of this difference could be due to the rare occurrence of follicular lymphomas in Iran and the fact that the majority of centroblastic /centrocytic types of lymphomas appear as follicular lymphomas. This subject needs to be further investigated, since there is scarce information in this area.

4. The male/female ratio of the distribution of non-Hodgkin's B-type low-grade and high-grade lymphomas was 1.7:1(M:F). At the Lymph Node Registry in Kiel, this ratio was 1.4:1, which is not significantly different.
5. With regard to age, in the later years of the fifth decade, there was a high occurrence of all non-Hodgkin's B-type lymphomas. In the early years of the sixth decade, low-grade B-type lymphoma had a high occurrence while high-grade B-type lymphoma had a high occurrence in the earlier stages of the fifth decade. But the figures of the Lymph Node Registry in Kiel showed that low-grade B-type lymphomas peak in the later years of the sixth and the beginning of the seventh decade. High-grade B-type lymphomas had a different pattern of occurrence. In general, the occurrence was higher in the first, second, third and seventh decades. Thus, in a comparison of the two countries it can be noted that the peak of low-grade B-type lymphoma is about one and a half to two decades earlier in Iran.
6. The most common site of involvement in all the samples was the cervical lymph nodes. This is equally true for low-grade and high-

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Table 5. Non-Hodgkin's lymphoma diagnosed on lymph nodes biopsies at the Lymph Node Registry in Kiel.

		Type of lymphoma			
B cell	No. (%)	T cell	No. (%)	Undefined	No. (%)
Low-grade malignant lymphomas	700 (54.5%)	Low-grade malignant lymphomas	114 (8.9%)		
Lymphocytic CLL, PLL, HCL	141, 2, 0 (11.1%)	Lymphocytic CLL, PLL	7, 3 (0.8%)		
Immunocytoma	158 (12.3%)	Small cell Cerebriform (mycosis fungoides and Sezary syndrome)	12 (0.9%)		
Plasmacytic	<7 (<0.5%)				
Centroblastic-centrocytic (cb/cc)	262 (20.4%)	Lymphoepitheloid (LeL)	8 (1.4%)		
Centrocytic	70 (5.4%)	AILD (Lgx) type	46 (3.6%)		
Monocytoid	6 (0.5%)	T-zone lymphoma	11 (0.9%)		
Borderline case	18 (1.4%)	Pleomorphic, small cell	17 (1.3%)		
Development into high-grade ML	17 (1.3%)				
Unclassified	19 (1.5%)				
High-grade malignant lymphomas	300 (23.4%)	High-grade malignant lymphomas	106 (8.2%)	64 (5.0%)	
Centroblastic	176 (13.7%)	Pleomorphic medium-sized and large cell	34 (2.6%)		
Immunoblastic	55 (4.3%)	Immunoblastic	14 (1.1%)		
Burkitt's lymphoma	33 (2.6%)	Large cell anaplastic	17 (1.3%)	9 (0.7%)	
Large cell anaplastic	1 (0.1%)	Lymphoblastic	41 (3.2%)	27 (2.1%)	
Lymphoblastic	11 (0.9%)	Unclassified		28 (2.2%)	
Unclassified	24 (1.9%)				
Total	1000 (77.9%)		220 (17.1%)	64 (5.0%)	

grade B-type lymphomas. This kind of involvement was similar to the findings in Kiel. It is necessary to note two interesting findings regarding the site of involvement. First, in 12 out of 31 cases of cervical lymph node lymphomas, the tonsils were affected with centroblastic lymphoma. Second, 13 out of 24 cases of Burkitt's lymphoma involved the abdominal organs.

7. The findings of the present study indicate that only 8.8% of non-Hodgkin's lymphomas were of the T-cell type and the most common lymphoma was the pleomorphic medium-sized and large cell lymphoma. In the Kiel findings,

T-cell lymphoma accounted for 17.1% of all lymphomas, which is double the percentage of our study. Also, the most common T-cell non-Hodgkin's lymphoma in the Kiel figures was a low-grade T-cell lymphoma of AILD (lgx) type whereas the most common T-cell lymphoma in the present study was a high-grade lymphoma. As indicated above, it is the high-grade type of T-cell lymphoma that predominates. In conclusion, the high-grade T-cell and B-cell lymphomas had the highest occurrence in Iran.

Section B

Comparison of the figures for Hodgkin's lymphomas in the present study with the figures

Table 6. Comparison of the distribution of all types of Hodgkin's lymphoma in Iran and western countries.

Histologic subtype of Hodgkin's lymphomas	Iran		West	
	No.	Percentage	No.	Percentage
Lymphocytic predominance	7	(12.8%)	55	(6%)
Lymphocytic depletion	3	(5.4%)	27	(2%)
Mixed cellularity	25	(45.4%)	272	(23%)
Nodular sclerosis	20	(36.4%)	628	(69%)
Total	55	(100%)	982	(100%)

belonging to the West,^{10,2} reveals the following differences and similarities:

1. The most common Hodgkin's lymphoma, based on the Rye classification, was mixed cellularity with about 45.4% in the present study whereas the most common Hodgkin's lymphoma was nodular sclerosis with 69.4% in western countries. The lymphocytic depletion type was 5.4% in the present study in comparison to 2%. This was the lowest occurrence of a type of Hodgkin's lymphoma in the series. Table 6 clearly shows the comparison between two other types of Hodgkin's lymphoma.
2. The gender ratio for the occurrence of Hodgkin's lymphoma in the present study and western studies were 1.6:1(M/F) and 1.7:1(M/F) respectively. There were however, two differences, which should be noted. First, in our findings men and women were similarly affected by the lymphocytic depletion lymphoma (the ratio being 1:1). Second, the western figures indicate that the ratio of women affected by nodular sclerosing is higher than men.
3. The average age of all types of Hodgkin's lymphomas, in sum and specifically, was in the fourth decade in our study. Western figures show that Hodgkin's lymphoma is more prevalent among young adults and the occurrence of the disease peaks in the late third and early fourth decades. Therefore, concerning age, our results are similar to those observed in the West.

From the above discussion, we conclude that lymphoma is common in Iran and that there appears to be similarities and differences between

Iran and western countries. Due to the existence of various classifications and high occurrence of lymphomas in Iran, more research should be conducted in this country. This will improve our diagnostic abilities and enable us to provide better management of the disease. The other advantage of using a unique classification is in setting up a common scientific language for the use of specialists. Questions such as why is there a high prevalence of high-grade T-cell and B-cell lymphomas? why are follicular lymphomas relatively rare in Iran? what can account for the higher prevalence of lymphomas in the Middle East and Iran are important questions which need to be answered.

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