

Original Article

Lymphomas in Iran

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Background: The present study aimed at examining the lymphomas in Iran.

Methods: This study was conducted in 1994 on patients' specimens who were referred to our centers during 1981 – 1994. Using the histochemical methods, the immunohistochemical markers were used to examine the biopsied specimens of 434 patients with non-Hodgkin's and Hodgkin's lymphomas. The patients were classified according to the updated Kiel and Rye classifications, respectively.

Results: Out of the 385 cases that were diagnosed as lymphoma, 277 had non-Hodgkin's and 108 had Hodgkin's lymphomas. Sixty-four point five percent of those with non-Hodgkin's lymphoma had the B type disease; 7.5% had the T-type; and the remaining 28% had Hodgkin's lymphoma. In the present study, most (48%) patients with Hodgkin's lymphoma had mixed cellularity whereas in western countries the most common type is reported to be nodular sclerosis (69.4%).

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 in Iran.

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Keywords: Hodgkin's lymphoma • immunohistochemistry • Iran • non-Hodgkin's lymphoma • lymphoma, classification

Introduction

Results of research conducted in the Middle East and Iran indicate a high incidence of lymphoma in the region.¹⁻³

In the first published statistics in 1965, Habibi showed that 8.4% of all cancers in Iran were malignant lymphomas.¹ The results of Habibi's study were further confirmed by Haghighi et al indicating that 7.6% of all the cancers in southern Iran were malignant lymphomas.⁴

High percentages of malignant lymphoma were reported from the Middle Eastern countries — 10.3% in Saudi Arabia, 13.5% in Iraq, and 11.7%

in Lebanon. In marked contrast, the findings of research conducted in the United States by the American Cancer Society, and in Denmark by International Agency for Research on Cancer, Lyon, France indicate that the percentage of malignant lymphomas, compared with other cancers, is 1.9% and 1.6%, respectively.

The high incidence of malignant lymphoma in Iran and the Middle East, compare western countries, calls for further research in this area, which remains relatively unexplored.

We conducted this study to explore the similarities and differences between western countries and Iran.^{5,6}

Materials and Methods

In the present study, 385 cases of malignant lymphomas — various types of Hodgkin's and non-Hodgkin's lymphomas — collected from seven diagnostic centers from Tehran, i.e., Shohada Hospital, Taleghani Hospital, Imam Hossein Hospital, Loghman Hakim Hospital, and

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Boo Ali Hospital; two private diagnostic centers, namely Armin Laboratory and Bank-e-Melli Hospital; and one hospital from Kerman Province were investigated. The study was conducted in 1994 on pathologic specimens of patients who were referred to the above-mentioned centers between 1981 and 1994. Additional clinical data, including age, gender, and site of sampling were recorded.

The primary diagnosis was made based on formalin-fixed paraffin sections of three-micron thick slides stained with hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Giemsa and silver and cholera acetate esterase. In those cases in which histochemical methods did not yield conclusive results, the diagnosis and 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^{2, 7, 8}:

KI1(pancytokeratin), CD45 (CLA), L26 (CD20), CD3, UchL1(CD45RO), β F1,K, λ , μ , Kis5, CD30, LMP, KiMIP, KiM4p,KiMy2, KiMy1, KiB5, Al, BcL2, S100, KiB3, and MT1.

Non-Hodgkin's lymphomas were marked based on the Kiel classification and Hodgkin's lymphomas marked based on the Rye classification. The frequency of occurrence of the lymphomas stratified by age, gender, and site of involvement was also noted.

Results

Three hundred and eighty-five cases out of 434 had malignant lymphomas of whom 277 cases had non-Hodgkin's lymphoma, 108 had Hodgkin's lymphoma, and the remaining (n = 49) could not be diagnosed as lymphoma for the following reasons:

1) The samples taken from 29 cases were of poor quality and unrecognizable, inadequate for diagnostic purposes, or were not from lymphatic tissues.

2) Nine cases were diagnosed as metastatic carcinoma of whom three had nasopharyngeal anaplastic carcinoma, two had oat cell carcinoma, three had metastatic carcinoma of unknown origin, and one had gastric adenocarcinoma.

3) Five cases revealed a hyper-immune reaction and chronic nonspecific lymphadenitis.

4) Five cases had myeloproliferative disorder.

5) One had embryonal rhabdomyosarcoma.

The distribution of B- and T-cell non-Hodgkin's and Hodgkin's lymphomas is shown in Table 1.

In the Kiel classification, the degree of malignancy of lymphoma is defined as "low grade" and "high grade." 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 lymphoma based on the Updated kiel classification.

Finally Table 4 indicates the distribution of Hodgkin's lymphoma based on the rye classification.

Discussion

To prepare the ground for comparison and discussion, it is necessary to present Table 5 the results on 1,284 cases consisting of all types of non-Hodgkin's lymphomas recorded at the lymph node registry in Kiel.⁶

A comparison between Tables 2, 3, and Table 5 (reproduced from Table 11 of Lennert and Feller's study in 1992) reveals the characteristics of non-Hodgkin's lymphoma and also the overall similarities and differences between lymphomas in Iran and the West.

The results of this comparison are presented 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 are 7.5% 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 with the West.

2- Considering the degree of malignancy, the majority (76%) of B-type lymphomas of the present study are high-grade lymphomas whereas with the Kiel studies, the majority (54.5%) of lymphomas were of the low-grade type. One reason for this difference could be due to the lower

Table 1. Distribution of types of lymphomas.

Type of lymphoma	No. of cases	Percentage
Hodgkin's lymphoma	108	28
Non-Hodgkin's lymphoma B-type	248	64.5
Non-Hodgkin's lymphoma T-type	29	7.5
Total	385	100

Table 2. Distribution of B-cell non-Hodgkin's lymphomas according to gender and age.

Subclass of malignant lymphoma	No. of cases	Percentage	M:F	Mean age (range)	Main site of involvement
Low-grade malignant lymphomas	59	24	2.3:1	50(18 – 80)	Cervical nodes (13)
CLL	11	4.5	3:1	58 (47 – 80)	Cervical nodes (3)
Hairy cell Lymph.	2	1	2:0	58 (55 – 61)	Cervical nodes (8)
IC	19	7.5	2.3:1	49 (21 – 75)	Vertebrae (2)
Plasmacytic	5	2	1.5:1	47 (20 – 69)	Abdomen (4)
Cb/CC	10	4	0.7:1	52 (25 – 70)	Cervical nodes (2)
CC (Mantle Cell)	4	1.5	2:0	48 (41 – 50)	Mesenteric nodes (2)
Monocytoid B-cell lym.	2	1	1:1	44 (32 – 56)	Duodenum (2)
IPSID*	3	1	2:1	48.5 (18 – 64)	Small bowel (1)
MALT (mentrocytoid)*	2	1	2:0	41.5 (30 – 53)	Large bowel (1)
MALT (IC type)*	1	0.5	0:1	53	Orbit (1)
High-grade malignant lymphomas	189	76	1.8:1	35.5 (1 – 90)	Cervical nodes (51)
Cb	114	46	1.8:1	46.5 (1 – 90)	Cervical nodes (47)
Ib	18	7	3:1	41.5 (4 – 73)	Abdomen (6)
Burkett's Ly.	36	14.5	2.3:1	15.5 (4 – 74)	Abdomen (21)
Lymphoblastic	11	4.5	0.:0.6	20 (2 – 54)	Axillary nodes (2)
Large CAL (Ki-1+)	1	0.5	1:0	52	Axillary nodes (1)
T-cell rich B-cell Lymph.	1	0.5	1:0	31	Axillary nodes (1)
H G SCL B-cell	3	1	1:2	43.5 (32 – 55)	Cervical nodes (2)
Lymph. of mediast	5	2	—	—	Bone marrow (2)
Unclassified lymph.	5	2	—	—	Bone marrow (2)
Total	248	100	2:1	44 (1 – 90)	Cervical nodes (64)

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

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 a 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 lymphomas in Iran because there is the possibility that high-grade lymphomas in Iran are of the primary type and that some important factors may play important roles in producing such a high incidence.

3- In the present study, the most common low-grade B-cell lymphoma was immunocytoma with 19 cases (7.5%) and the most common high-grade B-cell lymphoma was centroblastic lymphoma with 114 cases (46%). However, in the lymph node registry in Kiel, the most common low-grade lymphoma was centroblastic/centrocystic with 262 cases (accounting for 24.4%) 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 is 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, because the

majority of centroblastic/centrocystic types of lymphomas appear as follicular lymphomas. This is a subject that needs further investigation, since there has been little research done in this area.

4- The male:female sex ratio of distribution of non-Hodgkin's B-type low-grade and high-grade lymphomas is 2:1. This ratio at the lymph node registry in Kiel is 1.4:1. The difference, though not statistically significant, must be considered.

5- Regarding age, in the mid-stage of the fifth decade, there was a high incidence of non-Hodgkin's B-cell lymphomas. In the early stages

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

Subclass of malignant lymphoma	No. of cases	Percentage
Low-grade malignant lymphoma	5	17
Mycosis fungoid	1	3.5
Lymphoepitheloid lymph. (Lennert's Lymph.)	1	3.5
Angioimmunoblastic (AILDs, LgX)	2	7
Pleomorphic small cell	1	3.5
High-grade malignant lymphomas	24	83
Pleomorphic medium-sized and large cell	11	38
Immunoblastic	1	3.5
Large cell anaplastic (Ki-1+)	6	20.5
Lymphoblastic lymph.	6	20.5
Total	29	100

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

Subtype of Hodgkin's	No. of cases	Percentage	M:F	Mean age (range)
Lymph. predominance	12	11	2.7:1	30 (10 – 57)
Mixed-cell	52	48	2.7:1	32.5 (4 – 70)
Nodular sclerosis	33	30.5	1.8:1	34 (6 – 66)
Lymph. depletion	11	10	1:1	24.5 (6 – 57)
Total	108	100	2:1	30.5 (4 – 70)

of the sixth decade, low-grade B-cell lymphoma had a high incidence. High-grade B-cell lymphoma had a high incidence in the mid-stages of the fourth decade. The figures of the lymph node registry at Kiel,⁸ however, showed that low-grade B-cell lymphomas peak in the later stage of the sixth decade and earlier stage of the seventh decade. High-grade B-cell lymphoma had a different pattern of occurrence. In general, the occurrence was higher in the first, second, third and seventh decades. Thus, comparing the two statistics, it can be noted that the peak of low-grade B-cell lymphoma is one decade earlier in Iran and the peak of high-grade B-type lymphoma is about one and a half to two decades earlier.⁵

6- The most common site of involvement of all

samples was the cervical lymph nodes. That was equally true for low-grade and high-grade B-cell lymphomas. This was similar to the findings in Kiel. It is necessary to note that 21 out of 36 cases of Burkitt's lymphoma involved the abdominal cavity organs.

7- We found that only 7.5% of non-Hodgkin's lymphomas were of T-cell lymphomas. The most common T-cell lymphoma was the pleomorphic medium-sized and large-cell lymphoma. In comparison with the Kiel findings, T-cell lymphoma accounted for 17.1% of all lymphomas, which was double the percentage we found. Second, the most common T-cell non-Hodgkin's lymphoma in the Kiel figures was a low-grade T-cell lymphoma AILD (Lgx) type whereas the most

Table 5. Non-Hodgkin's lymphomas diagnosed on lymph nodes biopsies at the lymph node registry in Kiel.⁸

	B			T		Undefined No. (%)
	No.	%		No.	%	
Low-grade malignant lymphomas	700	54.5	Low-grade malignant lymphomas	114	8.9	
Lymphocytic			Lymphocytic			
CLL	141		CLL	7		
PLL	2	11.1	PLL	3	0.8	
HCL	0					
			Small cell-cerebriform (mycosis fungoides and sezary syndrome)	12	0.9	
Immunocytoma	158	13	Lymphoepitheloid (LeL)	8	1.4	
Plasmacytic	< 7	< 0.5	AILD (LgX) type	46	3.6	
Centroblastic-centrocytic	262	20.4	T-Zone lymphoma	11	0.9	
Centrocytic	70	5.4	Pleomorphic, small cell	17	1.3	
Monocytoid BC Lymph.	6	0.5				
Borderline case						
Development it high grade	18					
ML	17	4.2				
Unclassified	19					
High-grade malignant lymphomas	300	23.4	High-grade malignant lymphomas	106	3.2	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	1	0.1	Anaplastic	17	1.3	9 (0.7)
Lymphoblastic	11	0.9	Lymphoblastic	41	3.2	27 (2.1)
Unclassified	24	1.9	Unclassified			28 (2.2)
Total	1000	77.9		220	17.1	64 (5.0)

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

Histologic subtype of lymphoma	Iran	West
	No. (%)	No. (%)
Lymphocytic predominance	12 (11)	55 (6)
Lymphocytic depletion	11 (10)	27 (2)
Mixed cellularity	52 (48)	272 (23)
Nodular sclerosis	33 (30.5)	628 (23)

common T-cell lymphoma in our study was high-grade lymphoma. As indicated above, in the findings of the present study, the high-grade T-cell lymphoma predominated. In conclusion, we note that in general, in Iran, according to the findings of this study, the high-grade T-cell and B-cell lymphomas have the highest occurrence.

Section B

In comparison with the figures of Hodgkin's lymphomas of the present study with one of the figures of the western countries,^{9,10} the following differences and similarities were found:

1-The most common Hodgkin's lymphoma, based on the Rye classification, was mixed cellularity with a frequency of almost 48% in the present study whereas the most common Hodgkin's lymphoma was nodular sclerosis with a frequency of 69.4% in western countries. The lymphocytic depletion type was 10% in the present study and 2% in western countries. This was the lowest incidence of a type of Hodgkin's lymphoma in the comparison. Table 6 clearly shows the comparison between two other types of Hodgkin's lymphoma.

2- The gender ratio of the occurrence of Hodgkin's lymphoma in the present study with western studies^{9,10} was 1.6:1 (M:F) and 2:1 (M:F), respectively — men are more affected by Hodgkin's lymphoma than women. There were, however, two differences which should be noted. Firstly, we found that men and women were similarly affected by the lymphocytic depletion lymphoma (the M:F ratio being 1:1). Secondly, the western figures indicated that the number of women affected by nodular sclerosis is higher than men.

3- The average age for all types of Hodgkin's lymphomas and each type of Hodgkin's lymphoma was in the early fourth decade in our study. In the western figures,^{9,10} Hodgkin's lymphoma was more prevalent among young adults and the incidence of the disease peaked in the late third decade and early fourth decade. Our findings were therefore

similar to those observed in the West. This indicates that there are no significant differences based on age.

One similar study has been conducted in Iran by Tabei et al.⁷ That study, conducted in Shiraz University, investigated 294 cases of lymphomas from Fars and Khorasan solely based on the working formulation using H&E staining. They did not use immunohistochemistry and special histochemical stains. In addition, they did not differentiate between the distribution of non-Hodgkin's lymphomas of T- and B-cell types.

Compared with the above-mentioned study, the present study has investigated a larger sample, with more histochemical stains and immunohistochemical methods which has adopted the updated Kiel classification.

From the discussion above, we concluded that lymphoma is common in Iran and that there are similarities and differences between Iran and western countries based on type of lymphomas according to the Kiel and Rye classification. We also concluded that because of the existence of various classifications for lymphoma and high occurrence of lymphomas in Iran, we need more research for better recognition of lymphomas in Iran. This will improve our ability to diagnose lymphomas with greater precision and consequently will enable us to provide better treatment in Iran. The other advantage of using a classification is in setting up a common scientific language for the use of specialists in Iran. Questions such as why there is a high prevalence of high-grade T-cell and B-cell lymphomas or why there is the rare appearance of follicular lymphoma, and also why there is a higher prevalence of lymphomas in the Middle East and Iran are important questions which need further investigations.

While further research in this area is necessary for a better understanding of the underlying causes, a sound and acceptable classification is also needed for the better comparison between the findings of this study and other similar studies. Classifying various types of lymphomas is not an easy task, as there are seven classifications and one working formulation in use at present.¹¹ In this study, malignant lymphomas are classified using the updated Kiel classification, because it is based on cytomorphology, immunophenotyping, and cellular differentiation⁵ while other classifications, such as Rappaport's based purely on cytomorphology, lack this 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 the comparability between the results of our study and those of western countries which have used a similar classificatory system.

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