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A study of malignant lymphomas in Iran, based on the updated Kiel classification

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Summary. One hundred and sixty-two consecutive cases of malignant lymphoma were collected from two diagnostic centres in north and south Iran. Tissue samples were examined by immunohistological methods, and the non-Hodgkin's lymphomas were classified according to the updated Kiel classification. The distribution of the different types of malignant lymphoma in this study is compared with the situation in Western countries.

Key words: Hodgkin's and non-Hodgkin's lymphomas – Kiel classification – Immunohistochemistry – Iran

Introduction

Lymphoproliferative diseases may cause considerable diagnostic difficulties or even escape recognition. This uncertainty is reflected in the existence of divergent classifications and terminologies. Lymphoma classifications based purely on cytomorphology (Rappaport 1966) are being increasingly replaced by a more pragmatic terminology (Working formulation, Non-Hodgkin's Lymphoma Pathologic Classification Project 1982) or by a classification based on the morphology and immunobiology of the cells involved (Kiel classification; Lennert et al. 1975). In this classification reference is made not only to the morphology but also to the immunophenotype and the stage of differentiation within each lineage. Further, prospective studies have meanwhile defined each entity and established prognostic features (Brittinger et al. 1984).

Malignant lymphomas are a relatively common type of malignancy in the Middle East (Parkin et al. 1984). In Iran they account for 8.4% of all cancer cases (Habibi 1965). It is our aim to subclassify our cases of malignant lymphoma according to the updated Kiel classification (Stansfeld et al. 1988) and to compare the results with other similar studies.

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Materials and methods

One hundred and sixty-two consecutive cases of malignant lymphoma received as biopsy and surgical specimens from two diagnostic centres in north and south Iran (Tehran and Kerman) were collected and investigated. Some additional clinical data, including age, sex and site of sampling, were recorded.

The primary diagnosis was made mainly on conventional formalin-fixed paraffin sections stained with haematoxylin and eosin (H&E) and Giemsa. All cases were additionally reviewed and classified in the lymph node registry in Kiel under the auspices of Prof. K. Lennert. In this centre all cases were routinely stained with H&E, Giemsa, periodic acid-Schiff (PAS) and silver impregnation.

In a number of cases we also stained paraffin sections immunohistochemically, using monoclonal antibodies or polyclonal antisera to study the immunophenotype of the tumour cells. To differentiate lymphomas from other anaplastic tumours, we used common leucocyte antigen (CLA; Dianova, Hamburg, FRG) and KL1 antibody (Dianova), a pan-epithelial marker. To differentiate lymphomas from myeloproliferative diseases we used the chloroacetate esterase reaction (Leder 1964) and Giemsa staining. B-cell-associated surface antigens were studied with the monoclonal antibodies Ki-B3 (Feller et al. 1987), Ki-B5 (Hansmann et al., to be published), and L26 (Dakopatts, Hamburg, FRG). T-cell antigens were studied with MT1 (Eurodiagnostic, Giessen, FRG) and UCHL1 (Dakopatts). In addition, rabbit anti-human antibodies against kappa and lambda light chains (Dakopatts) were used to study the clonality of B cells. The monoclonal antibody Ber-H2 was used to study Reed-Sternberg cells in cases of Hodgkin's disease (Dakopatts).

Results

In this study we collected 173 consecutive cases from two diagnostic centres in Iran. After they had been reviewed and examined immunohistochemically in Kiel, 11 cases were omitted and 162 cases were classified as malignant lymphoma. Of the 11 cases that were omitted, 8 were because of poor technique (mostly poor fixation). Two cases were diagnosed as myeloproliferative disorder because of a positive reaction with chloroacetate esterase and the occurrence of cytoplasmic granules in Giemsa staining. One case was diagnosed as metastatic nasopharyngeal carcinoma in a cervical lymph node, as sus-

Table 1. Distribution of various malignant lymphomas in 162 cases studied

Type of lymphoma	No. of cases	Percentage
Hodgkin's disease	53	32.7
Non-Hodgkin's lymphoma, B-cell type	91	56.2
Non-Hodgkin's lymphoma, T-cell type	15	9.3
Unclassified high-grade lymphoma	3	1.8
Total	162	100.00

Table 2. Distribution of 53 cases of Hodgkin's disease

Subtype	Number of cases	Percentage	M:F	Median age, years (Range)
Lymphocyte predominance	5	9.4	4:1	30 (10–57)
Mixed cellularity	27	50.9	3.5:1	27 (4–60)
Nodular sclerosis	13	24.5	1.6:1	40 (16–45)
Lymphocyte depletion	8	15.1	1:1	20 (6–40)

pected on conventional staining while the case was being reviewed and proven by its positive reaction with the anti-keratin antibody KL1.

The classification of the 162 cases of malignant lymphoma is shown in Table 1. There were 53 cases of Hodgkin's disease (32.7%) with a male predominance of 2.3:1.0. The age curve showed a peak in the second decade, and the most common site was the cervical region. The proportions of the subtypes of Hodgkin's disease, using the nomenclature recommended in the Rye classification (Lukes et al. 1966), are shown in Table 2.

Based on the Kiel classification, 91 cases were diagnosed as non-Hodgkin's lymphomas of B-cell type (56.2%) and 15 cases as T-cell lymphomas (9.3%). Three cases of high-grade lymphoma (1.8%) remained unclassified. Twenty-five of the cases of B-cell lymphoma were classified as low-grade (27.4%), whereas 66 cases were classified as high-grade B-cell lymphomas (72.6%). Among the low-grade B-cell lymphomas, immunocytoma and centroblastic-centrocytic lymphoma were the most common types, with 7 cases each. These were followed by 5 cases of chronic lymphocytic leukaemia of B-cell type, 2 cases of centrocytic lymphoma, 2 cases of hairy cell leukaemia, and 1 case each of immunoproliferative small intestinal disease (IPSID), or α-chain disease, and plasmacytoma. The immunophenotype of our single case of IPSID was alpha$^+$, gamma$^-$, mu$^-$, kappa$^-$, lambda$^-$. Of the 66 cases of high-grade B-cell lymphoma, centroblastic lymphoma was the most frequent type, with 37 cases. Immunoblastic lymphoma accounted for 12 cases, closely followed by Burkitt's lymphoma with 11 cases. Table 3 summarizes additional data on the individual subclasses of B-cell lymphomas. T-cell lymphomas accounted for 15 cases (9.3% of the total number), with a very high male predominance of 14.0:1.0 and a median age cf 36 years (range 6–55). The distribution frequency of T-cell lymphoma subclasses is shown in Table 4.

Discussion

Malignant lymphomas are a relatively common malignancy in the Middle East, including Iran. Table 5 shows the frequency of non-Hodgkin's lymphomas in a few selected countries in East and West. According to Habibi (1965), 8.4% of all cancers in Iran are malignant lymphomas. A further study from Iran indicates that malignant lymphomas account for 7.6% of all malignancies in southern Iran (Haghighi et al. 1971). In an unpublished study of our own, malignant lymphomas make up 7% of all malignancies in south-eastern Iran (Kerman province).

Of the cases collected in this study, about one-third (32.7%) represented Hodgkin's disease, and 56.2% were classified as non-Hodgkin's lymphomas of B-cell type. T-cell lymphomas accounted for 9.3% of the cases. According to one report from Saudi Arabia, 43.8% of the cases were Hodgkin's lymphomas and 56.2% non-Hodgkin's lymphomas (Stirling et al. 1979). The most common subtype of Hodgkin's disease in our cases was mixed cellularity type, 50.9% of the cases of Hodgkin's disease being of this subtype. This correlates well with the above mentioned study from Saudi Arabia, in which the mixed cellularity type is given as the most common subtype with 60.7% of the cases of Hodgkin's disease.

Among the non-Hodgkin's lymphomas, low-grade B-cell lymphomas are clearly under-represented in our collection (27.4% of the B-cell lymphomas), compared with reports from Western countries. Low-grade B-cell lymphomas have been reported to account for 70% of the non-Hodgkin's B-cell lymphoma cases in the lymph node registry in Kiel (Lennert 1990). There may be various reasons for this difference. On the one hand, the low mean age of the population in Iran when compared with European countries might account for the low incidence of low-grade B-cell lymphomas in our collection. In addition, some of the low-grade B-cell lymphomas manifest themselves as leukaemia and are readily diagnosed by clinical haematologists in Iran. On the other hand, some cases of centroblastic-centrocytic lymphoma cause diagnostic difficulties and may be misinterpreted as reactive follicular hyperplasia. It is also possible that the large number of cases of centroblastic lymphoma in our collection represent cases arising secondary to unrecognized centrocytic-centroblastic lymphoma.

Another striking point is the lack of low-grade B-cell lymphomas of the mucosa-associated lymphoid tissue in our collection. Most probably we missed the cases of this recently described entity (Isaacson and Wright

Table 3. Distribution of 91 cases of non-Hodgkin's lymphoma of B-cell type according to the updated Kiel classification

Subclass	No. of cases	Percentage	M:F	Median age (Range)	Main site of involvement
Low grade					
CLL	5	5.5	4:1	52 (50–67)	Axillary lymph node 2/5,
Hairy cell leukaemia	2	2.2	2:0	58 (55–61)	Bone marrow 2/2
IC	7	7.7	5:2	44 (21–62)	Cervical 3/7, small intestine 2/7
Plasmacytic	1	1.1	0:1	20	Cervical lymph node 1/1
CB-CC	7	7.7	1.3:1	55 (25–70)	Abdominal tumour 4/7
CC	2	2.2	2:0	41.5 (41–42)	Cervical lymph node 1, Axillary lymph node 1
IPSID[a]	1	1.1	1:0	18	Duodenum
High grade					
CB	37	40.6	1.6:1	50 (3–86)	Neck 16/37
IB	12	13.2	1:1	37.5 (4–73)	Abdomen 6/12
Burkitt's lymphoma	11	12.1	1.7:1	7 (4–74)	Abdomen 8/11
LB	6	6.6	2:1	17 (6–30)	Axillary lymph node 2/6
Total	91	100.00			

CLL, Chronic lymphocytic leukaemia; IC, immunocytoma; CB-CC, centroblastic-centrocytic lymphoma; CC, centrocytic lymphoma; IPSID, immunoproliferative small intestinal disease; CB, centroblastic lymphoma; IB, immunoblastic lymphoma; LB, lymphoblastic lymphoma

[a] Not included in the Kiel classification

Table 4. Distribution of T-cell lymphomas according to the updated Kiel classification

Mycosis fungoides	1
Lymphoepithelioid lymphoma (Lennert's lymphoma)	1
Angioimmunoblastic (LgX)	2
Pleomorphic, medium cell	2
Pleomorphic, large cell	3
Immunoblastic	1
Large cell anaplastic (Ki1+)	3
Lymphoblastic	2
Total	15

Table 5. Relative frequencies of non-Hodgkin's lymphomas in selected countries in East and West

Location and period		Relative frequency %	Reference
Iraq (Mosul)	1971–1975	13.5	Majeed (1982)
Lebanon	1953–1960	11.7	Azar (1962)
Saudi Arabia (KSFH)	1979–1984	10.3	El-Akkad et al. (1986)
Iran	1948–1960	8.4	Habibi (1965)
India	1973–1975	2.3	IARC (1982)
Brazil (Sao Paulo)	1973	1.9	IARC (1982)
USA (est.)	1973–1977	1.9	American Cancer Society (1985)
Denmark	1968–1976	1.6	IARC (1982)

1983). Further study is required to elucidate the exact incidence of this entity in Iran.

As for hairy cell leukaemia, the diagnosis is the best made in bone marrow trephine biopsy specimens. Other tissue samples, especially lymph nodes, are of less diagnostic value. In bone marrow, however, other low-grade B-cell lymphomas (particularly immunocytoma), must be considered in the differential diagnosis. In cases of immunocytoma, especially in poorly preserved samples, lymphoplasmacytoid cells may have clear cytoplasm and may mimic hairy cell leukaemia. For an immunohistochemical demonstration of hairy cell leukaemia the monocyte, macrophage specific monoclonal antibody KiM1P is recommended (Radzun et al., unpublished data). This antibody detects hairy cells in formalin-fixed paraffin sections decalcified with 10% acetic acid. In our two cases we had no chance to prove the diagnosis with this antibody, because the samples had been decalcified with 5% nitric acid.

An entity well known to pathologists in Mediterranean countries is α-chain disease or IPSID. The low incidence of this disease in our collection might indicate that it has been decreasing in frequency during the last decade. Most probably improved socioeconomic conditions are responsible for this downward trend.

The frequency of our cases of high-grade B-cell lymphoma considerably exceeds the incidence reported from Western countries. Other authers have also stressed the prevalence of high-grade B-cell lymphomas in southern Iran (Tabai and Abdullahi 1987). The high percentage of high-grade B-cell lymphomas in Iran might be due to the extremely low incidence of low-grade cases. The most common high-grade lymphoma in our collection

was centroblastic (40.6% of the cases of non-Hodgkin's lymphoma).

Burkitt's lymphoma (non-African type) was also quite common among our cases of non-Hodgkin's lymphoma (12.1%). The most prevalent site for these cases was the abdominal cavity (8 of 11 cases). The age of the patients ranged from 4 to 74 years, but the median age was 7 years. Our findings on Burkitt's lymphoma agree well with other studies performed in Iran (Tabei and Abdullahi 1987). No investigation for systemic or tissue bound Epstein Barr virus infection was done in our cases. In a recent study from the Federal Republic of Germany analysing primary gastrointestinal lymphoma in patients under 18 years of age, Burkitt's lymphoma was found to represent the most frequent histological type, accounting for 75% (Takahashi and Hansmann 1990).

Among the high-grade B-cell lymphomas, lymphoblastic lymphoma appears to be under-represented in this study. This again can be explained by the role of clinical haematologists in its diagnosis.

Our results demonstrate obvious differences between the distribution of the various types of malignant lymphoma in this study and that in Western countries.

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References

American Cancer Society (1985) Cancer statistics 1985. CA 35:19–35

Azär HA (1962) Cancer in Lebanon and the Near East. Cancer 15:66–78

Brittinger G, Bartels H, Common H, et al. (1984) Clinical and prognostic relevance of the Kiel classification of non-Hodgkin lymphomas: results of a prospective multicenter study by the Kiel Lymphoma Study Group. Hematol Oncol 2:269–306

El-Akkad SM, Amer MH, Lin GS, Sabbah RS, Godwin JT (1986) Pattern of cancer in Saudi Arabs referred to King Faisal Specialist Hospital. Cancer 58:1172–1178

Feller AC, Wacker HH, Moldenhauer G, Radzun HJ, Parwaresch MR (1987) Monoclonal antibody Ki-B3 detects a formalin resistant antigen on normal and neoplastic B cells. Blood 79:629–636

Habibi A (1965) Cancer in Iran. A survey of the most common cases. J Natl Cancer Inst 34:553–569

Haghighi P, Nabizadeh I, Asvadi S, Mohallatee EA (1971) Cancer in southern Iran. Cancer 27:965–977

International Agency for Research on Cancer (1982) Cancer incidence in five continents, vol 4. IARC, Lyon

Isaacson PG, Wright DH (1983) Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 52:1410–1416

Leder L-D (1964) Über die selektive fermentcytochemische Darstellung von neutrophilen myeloischen Zellen und Gewebsmastzellen im Paraffinschnitt. Klin Wochenschr 42:553–554

Lennert K (1990) Histopathologie der Non-Hodgkin-Lymphoma. Springer, Berlin Heidelberg New York

Lennert K, Mohri N, Stein H, Kaiserling E (1975) The histopathology of malignant lymphoma. Br J Haematol 31 [Suppl]:193–203

Lukes RJ, Craver LF, Hall TC, et al (1966) Report of the nomenclature committee. Cancer Res 26:1311

Majeed AMA (1982) Cancer in Nineva province. Ann Coll Med Mosul (Iraq) 13:9–19

Parkin DM, Stjernswärd J, Muir CS (1984) Estimates of the worldwide frequency of twelve major cancers. Bull WORLD Health Organ 62:163–184

Rappaport H (1966) Tumors of the hematopoietic system. Atlas of tumor pathology, sect. 3, fasc. 8, Armed Forces Institute of Pathology, Washington D.C.

Stansfeld AG, Diebold J, Kapanci Y, Kelenyi G, Lennert K, Mioduszewska O, Noel H, Rilke F, Sundstrom C, Van Unnik JAM, Wright DH (1988) Updated Kiel classification for lymphomas. Lancet I:292–293, 603

Stirling G, Khalil AM, Nada GN, Saad AA, Raheem MA (1979) Malignant neoplasms in Saudi Arabia. Cancer 44:1543–1548

Tabei SZ, Abdullahi B (1987) Non-Hodgkin's lymphoma in Iran. Med J Islam Rep Iran 1:13–21

Takahashi H, Hansmann M-L (1990) Primary gastrointestinal lymphoma in childhood (up to 18 years of age). J Cancer Res Clin Oncol 116:190–196

The Non-Hodgkin's Lymphoma Pathologic Classification Project (1982) National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a Working Formulation for clinical usage. Cancer 49:2112–2135