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NON-HODGKIN'S LYMPHOMA IN IRAN

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ABSTRACT

Two hundred and ninety cases of non-Hodgkin's lymphoma from the Fars Province Cancer Registry and Mashad University Hospital were reviewed and classified according to the new International Working Formulation for clinical use. The cases fall into low-grade (35 male, 26 female), intermediate-grade (61 male, 26 female), and high-grade (84 male, 26 female) groups. Each group includes several morphologic subtypes which are discussed in detail. In general, lymphomas occurred more frequently in two age groups: 5-20 and 45-65 years. High-grade lymphomas were more common than either low or intermediate-grade types. Interestingly, a high incidence of Burkitt's lymphoma (non-African type) was observed (58 of 290 cases), which occurred most commonly in children under 14 years of age, with the abdomen as a preferred site. Follicular small cell cleaved lymphomas (nodular PDL) were rare in our cases, in contrast to that which is reported in other series. Several cases of lymphomas not included in the Working Formulation such as intermediate lymphocytic lymphoma and its follicular variant (Mantle Zone type) were also observed (15 male, 7 female).

INTRODUCTION

Classification of non-Hodgkin's lymphoma (NHL) still remains one of the most controversial subjects in medicine. Rappaport's classification[1] which has gained worldwide acceptance correlates well with clinical course and prognosis[2] and is easy to utilize by clinicians. This classification is based entirely on morphological grounds. However, significant advances in immunology necessitates new approaches which encompass morphology as well as a modern concept of immunology.

In recent years, several new classifications have been proposed,[3,4,5] two of which are based in part upon the recent developments in immunological markers.[4,5] By using such immunological markers, Lukes and Collins were able to show that cells which Rappaport categorizes under the heading of "histiocyte" are actually transformed lymphocytes, either B or T-cell type, and that true histiocytic lymphomas are rare.[4] After this discovery, at least five other classifications for non-Hodgkin's lymphomas have been proposed[3] and this has led to much confusion, especially for physicians unfamiliar with the various systems.

In an attempt to resolve these issues objectively, a working formulation was proposed by the National Cancer Institute on the basis of an international multi-institutional clinicopathological study of 1175 cases of NHL. It is believed that this new formulation will replace all existing classifications of NHL.[3]

Lymphoma is the second most common malignancy in southern Iran.[6] The purpose of this article is to review cases of NHL in Shiraz and Mashhad during an eight year period from 1977 to 1984, and classify them according to the Working Formulation in order to better understand the biological behavior of these tumors and develop new protocols for chemotherapy and follow-up in the future.

MATERIALS AND METHODS

234 cases of NHL registered from 1977 to 1984 in the Fars Province Registry and 143 cases of NHL from the Ghaem Medical School, Mashhad University of Medical Sciences, were reviewed. The histologic slides of nearly all cases were retrieved from the files of the pathology departments of the Shiraz and Mashhad University Hospitals. 87 cases were excluded because of lack of representative slides or poor quality of the

prepared sections.

For each case, an average of three slides were reviewed. All histologic sections were prepared from biopsies of surgically removed material and stained by routine hematoxyllin and eosin stain and observed under the light microscope. PAS and MGP (methgreen pyronin) stains were available in some of the cases, and performmed additionally for confirmation of immunoblastic sarcoma. The cases were classified according to criteria proposed in the new Working Formulation.[3]

RESULTS

The results of this study are shown in tables I and II. The data can be summarized as follows:

Low-grade Lymphomas

A) Small cell lymphocytic (WDL): 56 cases (20% of total cases), 31 male and 24 female, with an age range of 10 - 70 years.

B) Follicular small cell cleaved (nodular PDL): four cases (one percent of total), two male and two female, age range 45 - 65 years.

C) Follicular mixed small and large cell (nodular mixed lymphocytic-histiocytic): two cases, both male, age range 55 - 65 years.

Intermediate-grade Lymphomas

D) Diffuse mixed small and large cell type (diffuse lymphocytic-histiocytic): 16 cases (five percent of total), 15 male, one female, age range 20 - 65 years.

E) Diffuse small cell cleaved (diffuse PDL): eight cases (three percent of total), four male, four female, age range 40 - 60 years.

F) Diffuse large cell (diffuse histiocytic): 63 cases (20 percent of total), 42 male, 21 female, age range 4 - 75 years.

High-grade Lymphomas

G) Large cell immunoblastic (diffuse histiocytic): 18 cases, (six percent of total), 14 male, four female, age range 10 -60 years.

H) Lymphoblastic lymphoma: 32 patients, (10 percent of total), 26 male, six female. The age incidence had two peaks, one in the second and the other in the fifth decade. There was no mediastinal involvement.

I) Small cell non-cleaved (undifferentiated), Burkitt type: 58 cases, (20% of total), 42 males, 16 females were of this type. Most of them were under 14 years of age.

J) Small cell non-cleaved, non-Burkitt type: two cases, both in old age (45 - 65 years).

Miscellaneous

22 cases in our report (15 male, 7 female) fulfilled the morphologic criteria of intermediate lymphocytic lymphoma, which although not included in this formulation, has been shown to be a distinct clinicopathologic entity.[7] Most of these patients were in the higher age groups (45 - 65 years). Four cases were of the Mantle Zone lymphoma type,[8] and ten cases remained unclassified.

DISCUSSION

Classification of non-Hodgkin's lymphoma is one of the most controversial and confusing subjects in medicine. Rappaport's classification[1] is based entirely on morphological grounds. By use of immunologic markers, Lukes and Collins were able to show that the histiocytic lymphoma of the Rappaport classification consists of large cells which in most cases derive from transformed lymphocytes, while lymphomas of true histiocytic nature are rare.[4] According to Lukes and Collins, most lymphomas are B-cell type that originate mainly from lymphocytes of the germinal center of lymphoid follicles.[4] These lymphocytes fall into one of four groups as observed by light microscopy: small non-cleaved, small cleaved, large non-cleaved and large cleaved cells. In the Lukes and Collins classification, these are called follicular center cells[4] and Lennert groups these as centrocytic, centroblastic type.[5]

Rappaport's classification,[1] which is used universally in many parts of the world including Iran has been shown to correlate well with clinical course and prognosis.[2] Recent development of cell markers and specific monoclonal antibodies to B and T lymphocytes have proven this classification scientifically incorrect. This necessitates the use of a classification that encompasses morphology as well as recent advances in the field of lymphoma. Such a classification must be easy to understand and utilize by the clinician and be reproducaible by the pathologist.

Although at least six histopathologic classifications for NHL have been developed by several authorities, none of these fulfill the above criteria.[3] This diversity has also led to much confusion and controversy among physicians unfamiliar with the various systems. In an attempt to resolve these issues objectively, a working formulation was proposed by an international multi-institutional clinicopathologic study of 1175 cases of NHL sponsored by the National Cancer Institue.[3] This new formulation is thought to eventually replace all existing classifications for NHL.[3] In this formulation, all lymphomas are divided into low-grade, intermediate and high-grade groups according to prognosis. In general, follicular or nodular patterns have a more favourable prognosis than the diffuse variety.[1,3,9] This pattern is thought to be present only in B-cell lymphomas.[3,4,10] Our retrospective study on 290 cases of NHL and reclassification of these cases according to the new formulation revealed several differences with that which is reported from western countries in regard

Table I: Sex incidence in various groups of lymphomas.

LOW-GRADE LYMPHOMAS

WDL		Small cell cleaved (nodular PDL)		Follicular mixed small and large	
Male	Female	Male	Female	Male	Female
31	24	2	2	2	0

INTERMEDIATE-GRADE LYMPHOMAS

Diffuse mixed small and large cell		Diffuse small cell Cleaved (Diffuse PDL)		Diffuse Large cell	
Male	Female	Male	Female	Male	Female
15	1	4	4	42	21

HIGH-GRADE LYMPHOMAS

Large cell immunoblastic		Lymphoblstic lymphoma		Small non-cleaved type			
				Burkitt type		Non-Burkitt type	
Male	Female	Male	Female	Male	Female	Male	Female
14	4	26	6	42	16	2	0

to type and age distribution, which we feel deserve comment.

Low-grade Lymphomas

In previously reported series, approximately half of all non-Hodgkin's lymphomas are low-grade, with 70% having a pattern of nodular PDL, 25% follicular mixed small and large cell, and 5% a pattern of WDL.[11]

In the present study, low-grade lymphomas comprise 20% of all cases, with 90% having WDL, 7% nodular PDL, and 3% follicular mixed small and large cell patterns (Table III).

A) Small lymphocytic lymphoma (well differentiated lymphoma (well- differentiated lymphocytic lymphoma or WDL in Rappaport's classification).[1,3,10,11] The pattern is diffuse with effacement of architecture by small, round lymphocytes exhibiting slight variation in nuclear size and shape (Fig 1). This morphology is also applied to tissue manifestations of chronic lymphocytic leukemia.[10]

This lymphoma occurs in old age [10,11] and although it is infrequent in other reports,[11] it is the most common histologic feature in our low grade group. The age incidence (45-65 years) we observed was the same as in other series.

B) Malignant lymphoma, follicular small cell, cleaved type (nodular poorly differentiated lymphocytic lymphoma, nodular PDL in Rappaport's classification).[1,3,11]

The lymph node is replaced by follicles of uniform size (Fig 2). The cells are slightly larger than normal lymphocytes, with irregular nuclei and prominent in-

Table II: The prevalence of different subtypes of lymphoma according to sex and age groups.

	Age group		0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74
	WDL	M		2	2	2	5	12	5	5
		F		0	0	3	4	8	3	4
Low Grade	Small cell cleaved Follicular (N PDL)	M						1	1	
		F						0	2	
	S&L Follicular	M						1		1
		F						0		0
Intermediate Grade	S&L Diffuse	M			1	4	4	2	3	1
		F			0	0	0	0	1	0
	Small cell cleaved Diffuse (PDL)	M			1		1	2	1	1
		F					0	3	1	0
	Diffuse Large Cell	M	0	4	6	4	7	12	5	4
		F	1	0	2	3	4	5	4	2
High Grade	Large cell Immunoblastic	M		2	3	2	4	2	2	
		F			1	1	0	1	1	
	Lymphoblastic	M		8	4	5	3	3	3	0
		F		1	0	1	0	2	1	1
	Diffuse small cell non Cleaved Burkitt type	M	8	22	4	2	3	2	1	
		F	3	6	3	0	1	2	1	
	Diffuse small cell non cleaved Non-Burkitt	M			1				1	
		F			0				0	

Table III: Incidence of low-grade **lymphomas** in Iran as compared to previous reports.

	Previous reported incidence		Present Study	
	Precent of low-grade	Precent of total lymphomas	Percent of low-grade	Percent of total lymphomas
WDL (Small lymphocytic)	5%	2.5%	90%	17%
Follicular small cell cleaved (nodular PDL)	70%	37.5%	7%	1%
Follicular mixed small and large cell	25%	12.5%	3%	6.7%

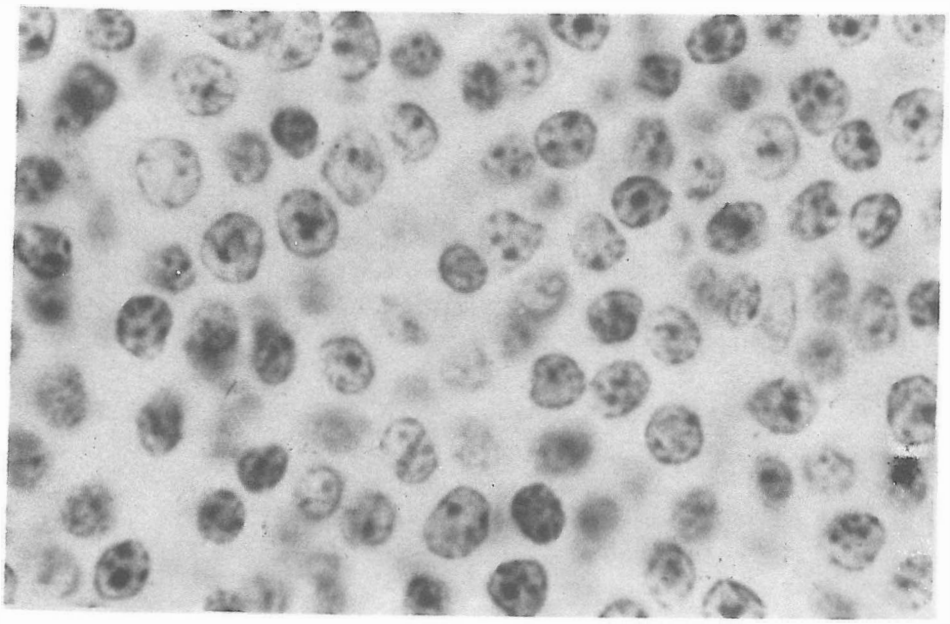

Fig.1 Diffuse pattern with effacement of general architecture of lymph node by small, round, well differentiated lymphocytes.

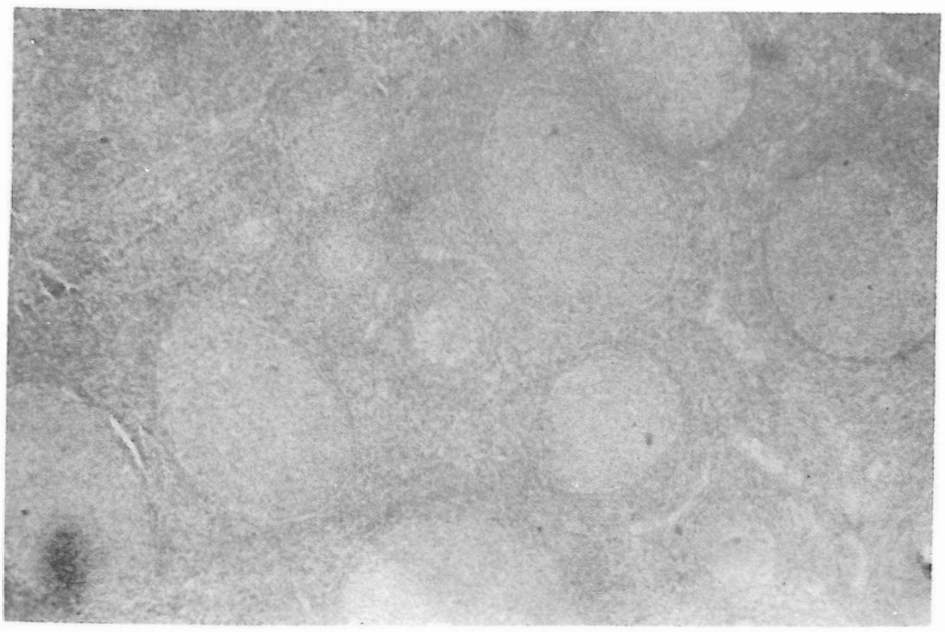

Fig.2 Low magnification shows a nodular pattern with nearly uniform size and shape of follicles.

dentation or cleavage planes (Fig 3). The chromatin pattern is coarse and nucleoli are small and inconspicuous. Cytoplasm is scanty and mitotic figures are rare. This pattern was found to be a less frequent type in our series, which is significantly different from that seen in other reports [11] (Table III). To date, we can not account for this obvious difference.

C) Malignant lymphoma, follicular mixed small cleaved and large cell type (nodular mixed lymphocytic type in Rappaport's classification). The architecture of the lymph node is nodular. There is no preponderance of one cell type over the other.

Intermediate-grade Lymphomas

D) Malignant lymphoma, follicular large cells type (nodular histiocytic lymphoma in Rappaport's classification).[1,3,4] The majority of cells within neoplastic follicles are of large cleaved or cleaved type, and mitotic figures are usually numerous. We did not find this type in our series.

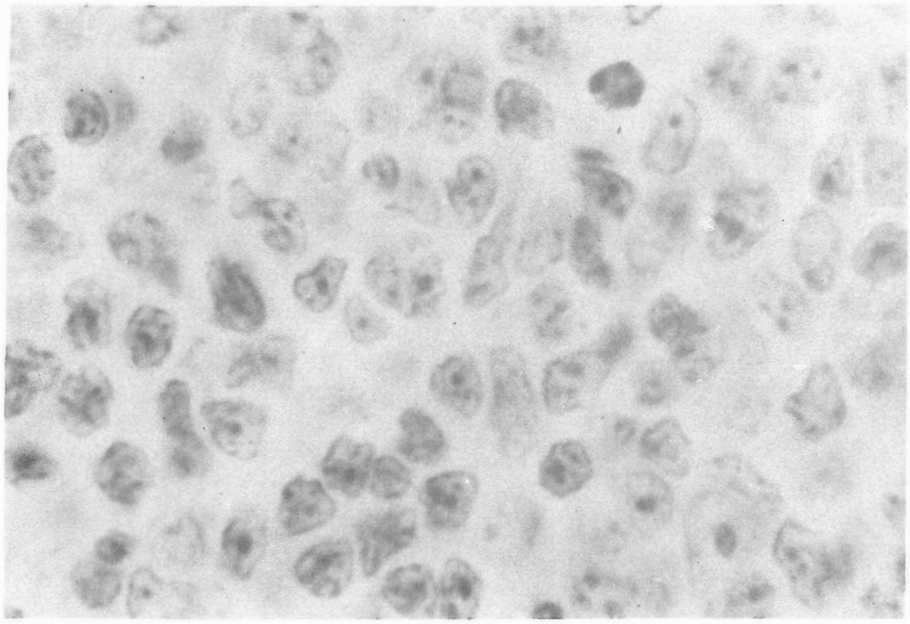

Fig.3 High magnification reveals cellular composition of follicles to be small cleaved lymphocytes.

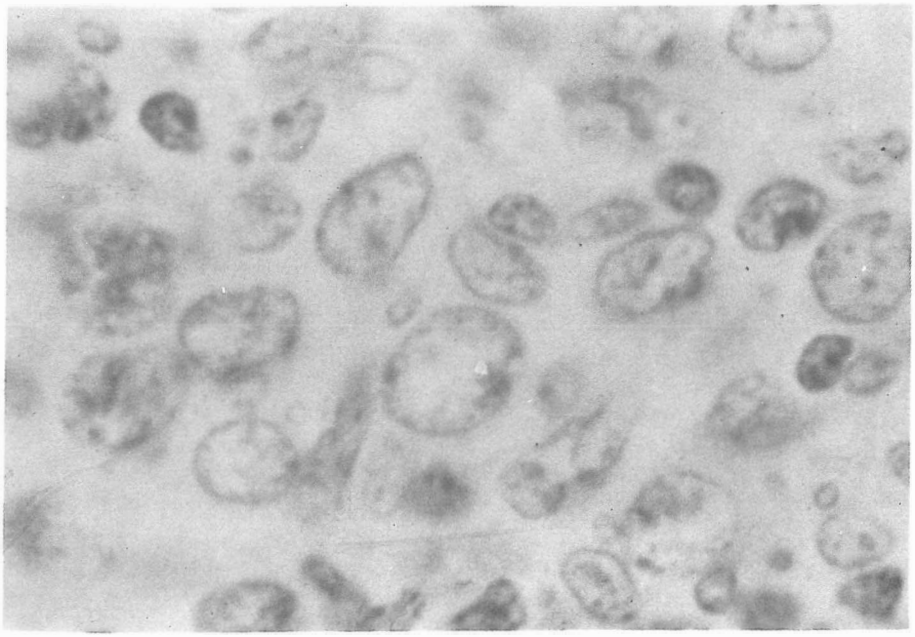

Fig.4 High magnification of malignant lymphoma, large cell type (large cleaved and non-cleaved lymphocytes).

E) Malignant lymphoma, diffuse small cell cleaved type (diffuse PDL in Rappaport's classification).[13] this represents the diffuse counterpart of the follicular small cell cleaved lymphoma. Mitotic figures are often more frequent than that observed in follicular type. The age incidence and prevalence of this type in our series were similar to that of other reports.[11]

F) Malignant lymphoma, diffuse mixed small and large cell type (diffuse mixed lymphocytic-histiocytic type in Rappaport's classification).[1, 5,12,13] This category represents a heterogenous group of lymphomas of mixed cellular composition. Some of these, in which small lymphocytes are of the cleaved cell type, could represent the diffuse counterpart of follicular lymphomas of mixed small and large cell type. Others may bear T-cell markers and could be classified under the heading of peripheral T-cell lymphomas.[12]

Still others may contain a higher content of epithelioid histiocytes and hence meet the criteria for Lennert's lymphoma.[13] In our cases, a few had light micros-

copic features of peripheral T-cell lymphomas, but due to lack of surface marker studies, this could not be proven with certainty.

G) Malignant lymphoma, diffuse large cell type (diffuse histiocytic lymphoma in Rappaport's classification).[1,3] The cells in this category, which are transformed B lymphocytes, may have cleaved or non-cleaved nuclei (Fig 4). The age incidence and prevalence in our cases were similar to that reported in other series.[11]

High-grade Lymphomas

High-grade lymphomas were common than low-grade and intermediate groups in our series and is comprised of the following types.

H) Malignant lymphoma, large cell immunoblastic type (diffuse histiocytic lymphoma in Rappaport's classification.[1,3,5,14] Immunoblasts have round to oval vesicular nuclei and one or more prominant centrally placed nucleoli which may be basophilic or eosinophilic. Immunoblastic lymphoma (also called immunoblastic sarcoma by Lukes and Collins[4]) can be of either B or T-cell origin.[14] The pattern is always diffuse.[4,14] This type occurs more commonly in old age. The age incidence and prevalence of this lymphoma in our series was the same as in other reports.[14]

I) Malignant lymphoma, lymphoblastic type. (lymphoblastic lymphoma in Rappaport's classification).[3,5,16] There is diffuse disruption of lymph node architecture. The lymphocytes have gray nuclei with finely distributed chromatin and inconspicuous nucleoli (Fig 5). The cytoplasm is scanty, and mitotic figures are frequent. Nuclei are larger than small lymphocytes and may or may not be convoluted. The "starry-sky" pattern is seen in 10% of cases.[3] This lymphoma originates from T-lymphocytes.[15] There is higher incidence in children and young adults.[15,16] The patients frequently present with a mediastinal tumour at the time of diagnosis.[15,16] The age incidence in our group is comparable to other reports[15,16] but there was no mediastinal involvement in our cases.

J) Malignant lymphoma, small cell non-cleaved type (undifferentiated Burkitt and non-Burkitt type in Rappaport's classification).[3,17,18,19] This pattern is characterized by diffuse involvement of the lymph node with cells having nuclei larger than those of small lymphocytes. The nuclei are uniform in size and usually round or ovoid in shape, with a coarse chromatin pattern. Two to five prominent nucleoli are evident (Fig 6). Each cell possesses a distinct rim of basophilic cytoplasm rich in RNA.

Mistoses are numerous and a "starry-sky" pattern is usually prominent (Fig 7). This pattern is produced by the appearance of large macrophages phagocytizing nuclear debris, interspersed between the small neoplastic cells. Lymphomas of small cell non-cleaved type showing nuclear pleomorphism and variation in size are designated as undifferentiated non-Burkitt type.[1,17,18,19]

Burkitt's lymphoma is the most common childhood lymphoma in Iran. It occurs mainly in children under 14 years of age and comprised 58 of 290 lymphomas in our study (incidence 20%). First described as a tumor of the jaw in African children,[17] it is now well known that Burkitt's lymphoma can occur in other parts of the world, as well as in western countries.[17,18,19] In non-African Burkitt lymphoma, abdominal involvement is the most common mode of presentation.[18,19] The majority of our cases presented with an abdominal mass (non-African type). The complete study of Burkitt's lymphoma in southern Iran is presently the subject of another report. There are subdivisions of lymphomas such as Intermediate Lymphocytic Lymphoma (ILL)[7] and its follicular variant mantle Zone (MZL) type,[8] which are not included in the new Working Formulation, but have been shown by several clinicopathologic studies to be distinct entities.[7,8] Intermediate lymphocytic lymphoma was first described by Barard et al[7] as a diffuse lymphoma, occuring in old age and composed of a mixture of small lymphoid cells, some having round nuclei similar to PDL. This lymphoma occurs in old age and has a course comparable to that of diffuse PDL.[7] Immunological studies have suggested that the cells may arise from lymphocytes or primary follicles or the mantle zone of secondary follicles.[7,8] A follicular variant of ILL known as Mantle Zone Lymphoma is also described in which atypical lymphoid cells morphologically similar to those described in ILL proliferate as a wide mantle around non-neoplastic atrophic germinal centers, imparting a nodular pattern at low magnification in light microscopy. This type has a more favorable course than ILL.[8] Ninteen cases in our series (13 male, 6 female) all in the upper age group (45-60 years) belong to this group, four of which were of MZL type. Ten cases remained unclassified.

In conclusion, lymphoma is the second most common malignancy in Iran. Two peak incidences are seen at 5-20 and 40-60 years. The majority of cases were seen in males (M/F 2:1). Our studies showed that high-grade lymphomas are seen more frequently than low and intermediate types in this part of the world. The Burkitt lymphoma, a unique type of lymphoma from a geographical point of view, is seen frequently in children and presents predominantly with abdominal signs and symptoms (non-african type).

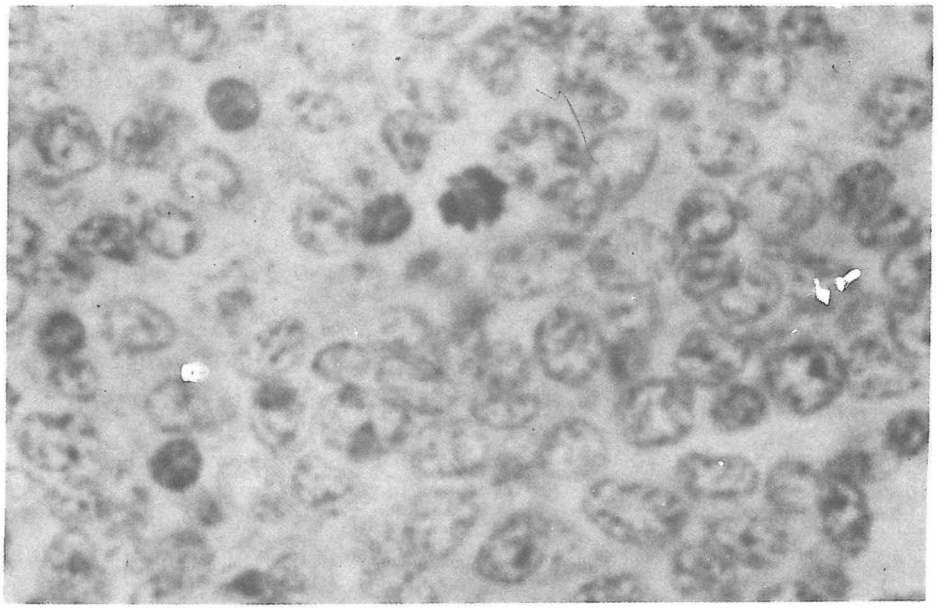

Fig.5 High magnification of malignant lymphoma, lymphoblastic type. The lymphocytes have a nucle us with finely distributed chromatin and scanty cytoplasm. Mitosis is seen.

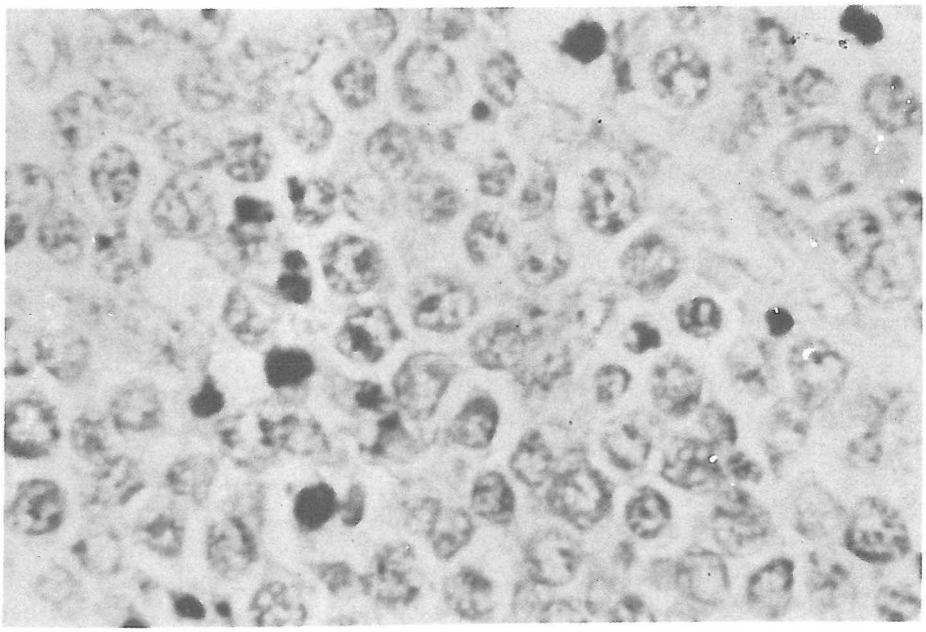

Fig.6 Burkitt's lymphoma, diffuse pattern. The cellular component is comprised of small non-cleaved lymphoeytes. A macrophage with clear cytoplasm is seen.

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