Malignant lymphoma in Al-Qassim, Saudi Arabia, reclassified according to the WHO classification

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ABSTRACT

الأهداف: تحديد مدى تكرار الأنواع المختلفة من الأورام الليمفاوية (ML) في منطقة القصيم بالمملكة العربية السعودية على حسب التقسيم الحديث لمنظمة الصحة العالمية (WHO).

الطريقة: تناولت هذه الدراسة الحالات التي تم جمعها مسبقا وكانت العينات المتاحة لـ385 من أصل 519 حالة تم تشخيصها كأورام ليمفاوية (ML) منذ عام 1988م وحتى عام 2007م. تم فحص تلك الحالات على حسب شكل الخلايا ثم تبع ذلك الفحص بالصبغات الهستوكيميائية المناعية باستخدام مجموعة من مضادات الأجسام. وقد تم إجراء الدراسة في مركز الأمير فيصل للأورام (PFOC) بمستشفى الملك فهد التخصصي (KFSH) – بريدة – القصيم – المملكة العربية السعودية.

النتائج: تبين لنا من خلال مراجعتنا أنه من أصل 385 حالة كان هناك: 251 (65.2%) حالة أورام من نوع الغير هودجكين (NHL)، 117 (30.4%) من نوع الهودجكين (HL)، كانت نسبة الذكور للإناث (1.6:1) مع تفاوت في العمر مابين 6 أشهر وحتى 103 عام. أورام الخلايا (B) كانت الأكثر شيوعا بين الأورام من النوع الغير الهودجكين (NHL) (81.6%)، ويعتبر النوع ذو الخلايا الكبيرة المنتشرة (DLBCL) هو الأكثر شيوعا حيث كانت نسبته (50.1%)، بينما الليمفوما الأقل خطورة مثل نوع الحويصلي (FL) والليمفوما ذات الخلايا الصغيرة (SLL) هي الأقل شيوعا(13.2%). كانت أورام الخلايا (T) تمثل نحو (18.3%) من الأورام غير الهودجكين (NHL). وكما وجدنا أن النوع التليفي التكوري هو الأكثر شيوعا بين أورام الهودجكين الكلاسيكي (NSCHL) بنسبة (68.3%).

خاتمة: تعتبر الأورام من النوع الغير هودجكين (NHL) هي الأكثر شيوعاً في منطقة القصيم من المملكة العربية السعودية، وكان أكثرها انتشارا هو النوع ذو الخلايا الكبيرة المنتشرة (DLBCL) على خلاف ما يوجد في المناطق الأخرى من المملكة والشرق الاوسط، وكان نوع الهودجكين الكلاسيكى (NSCHL) هو أكثر الأورام اللمفاوية (HL) شيوعا.

Objectives: To determine the frequency of various types of malignant lymphoma (ML) in the Al-Qassim region of Kingdom of Saudi Arabia (KSA) according to recently introduced the WHO classification.

Methods: For this retrospective analysis, material was available in 385 out of 519 cases diagnosed as ML from 1988-2007. Morphological assessment was followed by immunohistochemistry using a panel of antibodies. The study was conducted at Prince Faisal Oncology Centre (PFOC) of King Fahad Specialist Hospital (KFSH), Buraidah, Al-Qassim, KSA.

Results: Out of 385 cases reviewed, 251 (65.2%) had non-Hodgkin lymphoma (NHL) and 117 (30.4%) had Hodgkin lymphoma (HL). Male preponderance (male to female ratio 1.6:1) and a wide age range was observed (6 months to 103 years). B cell neoplasms were the most common NHL seen (81.6%) and diffuse large B cell lymphoma (DLBCL) was the most frequent type of NHL encountered (50.1%). Indolent lymphomas like follicular lymphoma (FL) and small lymphocytic lymphoma (SLL) were rather uncommon (13.2%). T cell lymphoma comprised 18.3% of the NHL. The most common type of HL was nodular sclerosis classical Hodgkin lymphoma (NSCHL) (68.3%).

Conclusion: In Al-Qassim region of KSA, NHL is the most common ML seen and DLBCL the most common type. Unlike other parts of KSA and Middle East, NSCHL is the most common type of HL encountered.

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Geographical variation in the distribution of different histological types of lymphoid neoplasms, which comprise a diverse yet closely related group of neoplasms, is well known.[1] Over the past decade, the WHO classification and categorization of lymphoid neoplasms, which is based on morphology, immunophenotyping, cytogenetic, and molecular characteristics, as well as clinical behavior and some known aspects of etiology and pathogenesis have been firmly established and replaced the previous classifications based on morphology.[2] With the introduction of this classification of lymphoid neoplasms, it is important to revisit epidemiology of lymphoma in different regions of the world. Kingdom of Saudi Arabia is the largest among Middle East countries and Al-Qassim, an arid desert with patches of oasis, is in its central region. The population of Al-Qassim is approximately one million. Malignant lymphoma (ML) is one of the most common malignant neoplasms in Al-Qassim.[3,4] A retrospective study of the pattern of lymphoma based on working formulation from this region has been previously published.[4] This report presents a series of 366 cases of ML from the Al-Qassim region, KSA classified according to WHO classification.

Methods. The King Fahad Specialist Hospital is a tertiary care referral centre, which has the only oncology centre of the region, the Prince Faisal Oncology Centre (PFOC), Buraidah, Al-Qassim, KSA. Hence, almost all cases of ML are seen here. A retrospective analysis was conducted on 519 consecutive cases of lymphoproliferative disorders (LPD), diagnosed over a period of 20 years (1988-2007) in this institution. Only cases where formalin processed paraffin tissue blocks were available for immunohistochemical (IHC) study were included (385/519). All those cases that did not have formalin processed paraffin tissue blocks available were excluded from further study (134/519). Cases with a diagnosis of plasmacytoma, Langerhan's granulomatosis, and atypical lymphoid hyperplasia were also included in the study. Clinical information relating to age, gender, and location of the disease at presentation were recorded. Three micron thick tissue sections were obtained from paraffin blocks and stained with hematoxylin and eosin. Slides were histologically examined, and ML was first categorized based on morphological findings. Immunohistochemical staining was performed on the paraffin sections, using microwave heat for antigen retrieval and streptavidin – biotin peroxidase method, with routine use of selected panel of monoclonal antibodies against CD 45 (LCA), CD 20, CD 3, CD 5, CD 10, CD 15, CD 21, CD 21, CD 23, CD30, CD 56, CD 68, Bcl2-antigen, Cyclin-D1, ALK1, Tdt, and epithelial membrane antigen (EMA) (Novocastra Newxastle, UK and Dako, Denmark). The LCA was used in all the cases and further antibodies were selected according to the morphological diagnosis (**Table 1**). All lymphomas were classified as Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), or histiocytic/dendritic cell neoplasm. The lymphoproliferative lesions, which defied unequivocal identification as ML, were diagnosed as atypical hyperplasia. The reproducibility of the diagnosis was confirmed by the reassessment of another histopathologist.

Results. Out of the 385 cases reviewed, 251/385; (65.2%) had NHL, 117/385 (30.4%) had Hodgkin's disease, 9/385 (2.3%) had histiocytic/dendritic cell neoplasm, and 8/385 (2%) had a diagnosis of atypical hyperplasia. We observed a male preponderance (221 males and 139 females; male to female ratio 1.6:1, data on gender was not available in 8 patients) and a wide age range (6 months to 103 years; mean age 43 years, age was not recorded in 7 cases). Out of the 251 patients with NHL, 205/251 (81.6%) were immunophenotyped as B-cell neoplasm. **Table 2** shows the age distribution of different types of B cell neoplasms according to WHO classification. Diffuse large B cell lymphoma (DLBCL) was the most common type 127/251 (50.1%) with the mean age of 50 years at diagnosis. Among DLBCL, 12 cases of T cell rich B cell were identified, which is a major mimic of HL. It was more common in males (male to female ratio 3:1) and occurred at a younger age (age range 16-40 and mean age of 32 years). All 8

Table 1 - Panel of monoclonal antibodies used in different morphological groups.

Morphological type	Antibodies
Indolent small cell lymphoma SLL, MCL, MZL, LPL	LCA, CD20, CD3, CD23, CD5, Cyclin D1.
Follicular lymphoma	LCA, CD20, CD21, CD10,BCl2
Lymphoma with blastic morphology LBL, BL	LCA, CD20, CD3, CD10,Tdt.
Diffuse large cell lymphoma	LCA, CD20, CD3, CD10, BCl2, CD30
Diffuse mixed cell and lymphoma with very large cells. HL, ALCL, TCRBCL,	LCA, CD20, CD3, CD15, CD30, CD56, ALK-1, EMA.
Histiocytic and dendritic cell neoplasm	LCA, CD68, CD1a, S-100.

SLL-Small lymphocytic lymphoma, MCL-Mantle cell lymphoma, MZL-Marginal zone lymphoma, LPL-Lymphoplasmacytic lymphoma, LBL-Precursor cell blastic lymphoma, BL-Burkitt's lymphoma, HL-Hodgkin's lymphoma, ALCL-Anaplastic large cell lymphoma, TCRCBL-T cell rich B cell lymphoma.

Table 2 - Age distribution, mean age and gender ratio of B-cell non-Hodgkin's lymphoma. Age was not recorded in 2 cases of diffuse large cell B-cell lymphoma and one case of follicular lymphoma.

Type of neoplasm	Age group									Total	Mean age	M:F
	≤10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	>80			
DLBCL	1	10	12	22	14	20	18	19	9	**125**	50	1.2
SLL				1	1	2	4	5	4	**17**	73	3.0
Follicular lymphoma			1	1	5	2	2	3	1	**15**	58	1.1
Plasmacytoma				1		1	6		2	**10**	54	7.0
EN-MZL				1		3	7			**11**	61	1.3
Burkitt's lymphoma	6	2								**8**	10	5.0
M(T)LBCL		1	4							**5**	22	0.6
MCL				2	2					**4**	43	4.0
Others			1	3	2				1	7		
Total	**7**	**13**	**18**	**31**	**24**	**28**	**37**	**27**	**17**	**202**		

DLBCL - diffuse large B cell lymphoma, SLL - small lymphocytic lymphoma, EN-MZL - extra nodal marginal zone lymphoma, M(T)LBCL - mediastinal (thymic) large B cell lymphoma, MCL - mantle cell lymphoma

Table 3 - Age distribution, mean age and gender ratio of B-cell non-Hodgkin's lymphoma and one case of follicular lymphoma.

Type of neoplasm	Age group									Total	Mean age	M:F ratio
	≤10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	>80			
TLBL	6	2	2				1			**11**	18	4
Mycosis fungoides			3	1	1					**5**	33	0.6
C-ALCL		1	1	1			2			**5**	41	3
Lymphomatoid papulosis			1							**1**	28	M
N-NK-cell			2							**2**	26	M
SPTCL		1								**1**	19	F
AITCL						4		1		**5**	62	M
PTCL NOS			1		2	2	1	1	1	**8**	58	3.0
ALCL		3				1	1	2	1	**8**	55	1.3
Total	**6**	**7**	**10**	**2**	**3**	**7**	**5**	**4**	**2**	**46**		

TLBL - T cell lymphoblastic lymphoma, C-ALCL - cutaneous anaplastic large cell lymphoma, N-NK-Cell - nasal and nasal type NK/T cell lymphoma, SPTCL - subcutaneous panniculitis-like T cell lymphoma, AITCL - angioimmunoblastic T cell lymphoma, PTCL NOS - peripheral T cell lymphoma not specified, ALCL - anaplstic large cell lymphoma, M-all males, F-all females.

Table 4 - Age related distribution of various types of Hodgkin's lymphoma. Age was not recorded in 4 cases; 2 each from MCCHL and LDCHL.

Type of neoplasm	Age group									Total	Mean age	Mate to female ratio
	≤10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	>80			
NLPHL	1	3	2	3						**9**	24	3:5
NSCHL	8	31	21	3	7	2	3	2	3	**80**	25	1.5
MCCHL	2	3		3	3		1	2		**14**	35	2.5
LRCHL	4	1		2	1	1				**9**	23	2.5
LDCHL					1					**1**	42	2.5
Total	**15**	**38**	**23**	**11**	**12**	**3**	**4**	**4**	**3**	**113**		

NLPHL - nodular lymphocyte predominance Hodgkin lymphoma, NSCHL - nodular sclerosis classical Hodgkin lymphoma, MCCHL - mixed cellularity classical Hodgkin lymphoma, LRCHL - lymphocyte rich classical Hodgkin lymphoma, LDCHL - lymphocyte depleted classical Hodgkin lymphoma.

cases of Burkitt's lymphoma (BL) were seen in children and young adults, (mean age 10 years; range 6-17 years) with a high male to female ratio of 5:1. Out of the 35 patients with indolent B-cell lymphoma, SLL was most common, followed by FL (follicular lymphoma) **Table 2**. Grade 3 lymphoma was seen more frequently in our series (9/16; 56.2%). Extra nodal involvement was seen in 106/205 (51.7%) cases of B-cell neoplasms. Forty-six cases of T-cell lymphoma were identified, which comprised 12% of all ML (46/385; 11.94%) and 18.3% of NHL (46/251). **Table 3** shows the age related distribution of various T cell lymphomas (TCL). Of these, 11/46 (23.9%) were precursor T-LBL and 11 (23.9%) were cutaneous TCL (5 mycosis fungoides, 5 C-ALCL, and one lymphomatoid papullosis). Peripheral T-cell lymphoma not specified and angioimmunoblastic T-cell lymphoma affected mainly adult and older patients, mean age 58 years (range 27-85 years), and mean age 62 years (range 55-80 years) respectively. In patients younger than 20 years of age, HL was the most common lymphoma 61.6% (53/86, total number of patients between the age group of 0-20 years). T cell lymphoblastic accounted for most of the TCL among children, 8 patients were under the age of 16 years. There was a distinct predilection of male gender 2.5:1 in TCL, except mycosis fungoides which had a female predominance (M:F = 0.6:1). Out of 117 cases of HL, 108/117 (92.3%) had classical Hodgkin lymphomas (CHL) and nodular sclerosis classical Hodgkin lymphomas (NSCHL) is the most common histological type (80/117; 68.3%) (**Table 4**). Male preponderance was noted in 73 males (73/117; 62.4%) and 40 females (40/117; 34.2%, gender was not recorded in 4 cases). **Table 4** shows the age related distribution of various types of HL. Extra nodal involvement was seen in 3 patients of CHL; 2 in stomach and one in pharynx. As can be seen in **Table 4**, 77% of our cases of HL were in the age group of 40 years or younger. In patients younger than 20 years of age, HL was the most common lymphoma (53/86; 61.6%) followed by B cell lymphoma (20/86 [where the 86 came from]; 23.3%) and T cell lymphoma (13/86; 15.1%).

Discussion. Since KFSH, PFOC receive most of the patients diagnosed with ML in different parts of Al-Qassim region, our study is representative of the population of this region. In the present series, diagnosis of ML was based on morphological, immunophenotyping, and relevant clinical information. These together are reported to have an accuracy of around 85%.[5] We have found NHL (65.2%) to be more common than HL (30.4%) and B cell neoplasms predominated in our series (53.2%). Indeed, despite considerable geographical variation, B-cell neoplasms are by far the most common type of lymphoid neoplasms seen all over the world. The highest incidence has been reported from Western Europe and among Whites in the USA.[1,5,6,7] The high proportion of B cell neoplasms observed by us is similar to the international lymphoma study group report, which has also been reported by different authors from other countries of this region.[6,8-14] As in the other Middle East countries, the relative frequency of DLBCL was the highest. DLBCL accounted for almost half of the NHL and 80% of B cell neoplasms in the present series. The mean age at presentation was 50 years. On the other hand, FL was rather uncommon in Al-Qassim region (<7% of all B cell neoplasms). Most of the studies from other areas of the Middle East have demonstrated a similarly low relative frequency of FL. However, a recent study from Jordan did show an unusually high relative frequency of FL.[10] It is possible that the age structure of a particular population affects the relative frequency of various types of ML.[15] In this context it may be interesting to note that while 63.2% cases of DLBCL were younger than 60 years of age, 59.4% of patients of FL and SLL were more than 60 years old.

Tcell neoplasms are not as common in this region as in East Asia and Far East countries.[16-20] These constituted around 18% of all NHL in our series, a finding in conformity with the previously reported experience from other areas of the Middle East .[8-14] Like NHL, the relative frequency of HL also varies within regions and among countries. The relative frequency of HL is the lowest in the Far East, Taiwan (3.2%) Japan (5%) South Korea (5.4%) Thailand (7.9%), Hong Kong (9.2%) and Malaysia (13.3%).[16-21] The relative frequency gradually increases as we move towards the West via Middle East; Jordan (21.6%), present series (32%), Iraq (33.6%), Egypt (35%).[8,10] However, relatively higher frequencies of HL have been reported from Libya (43%), UAE (41%) and previously from Al-Qassim (37.4%).[1,8,9] We have once again seen a high relative frequency of NSCHL (68.3%) in this series. Unlike other regions of KSA, where MCCHL is the most common type of HL, we had previously reported a higher relative frequency of nodular sclerosing type of HL from Al-Qassim region.[1] A recent study from KSA,[22] has reported a change in the type of HL seen in the rest of the country and NSCHL is gradually becoming the more frequent type seen.A similarly high frequency of NSCHL has been reported from UAE, Kuwait and the USA .[7,9,14] The majority of our HL patients were young, a factor which might contribute to a higher proportion of NSCHL.[15] However, a major limitation of our study is the non availability of formalin processed paraffin tissue blocks in nearly 26% of our patients. This might have affected

the overall frequency of different immunophenotypes, and the relative proportion thereof.

In conclusion, the current study is a report of a series of ML classified in accordance with the WHO scheme from KSA. The distribution of various types of NHL is in accordance with the majority of Asian studies, including low percentage of FL and indolent lymphomas, and a high proportion of aggressive B cell lymphoma. The incidence of T-cell lymphoma is much lower than the frequency reported from East Asian countries. The frequency of HL and distribution of its histological subtypes is comparable to data reported from the West, however, with a marked predominance of NSCHL.

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