RESEARCH COMMUNICATION

Clinico-Pathological Pattern of Extranodal Non-Hodgkin's Lymphoma in Saudi Arabia

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Abstract

Objectives: The incidence of primary extranodal non-Hodgkin's lymphoma (NHL) is variable in different regions of world but there is a paucity of literature on various demographic aspects of extranodal NHL as a group. This study was conducted to evaluate the clinico-pathological pattern of extranodal NHL in Saudi patients. Methods: We retrospectively studied a cohort of 855 NHL patients in four tertiary care centres in Riyadh, Saudi Arabia over a period of 5 years. Results: Extranodal NHL constituted 41.4% of the total. The mean age of affected patients was 55±18 years and a male to female ratio of 1.5:1.0. Most presented in the age range of 41-60 years. NHL of gastro-intestinal (GI) tract was the most common extranodal variety, followed by head and neck NHL (18%), primary cutaneous lymphoma (14.4%), primary CNS lymphoma (5.6%), and primary bone, thyroid and soft tissue lymphoma (4.5% each). In the GI tract, stomach was the most common site involved, accounting for more than 81% of GI NHL. Diffuse large B-cell lymphoma was the most common histologic type, comprising around 72% of all extranodal lymphomas. Conclusions: Extranodal NHL is common in Saudi Arabia and diffuse large B cell lymphoma is the most common histologic subtype. We found significant differences in the pattern of extranodal NHL in Saudi patients compared to those reported from other parts of the world. Further studies focused on the risk factors and treatment outcome are needed to better understand the biology of a disease common in this population.

Keywords: non-Hodgkin's lymphoma - extranodal sites - clinico-pathological pattern - Saudi Arabia

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Introduction

Non-Hodgkin's lymphoma (NHL) is a group of lymphoproliferative malignant disorders with heterogeneous histological and clinical characteristics (Evans et al., 2003). During the last few decades, there has been an increase in the incidence of NHL worldwide, including extranodal NHL, with an annual rise of 1-2% (d'Amore et al., 1991; Gurney et al., 2002; Muller et al., 2005). This increase is more prominent in the Asian and black populations and for the aggressive NHLs (d'Amore et al., 1991; Muller et al., 2005). NHL is one of the most common type of cancer in Saudi Arabia and ranked second (7.9%) among all cancers in the year 1999-2000 and third (7.7%) in 2007 (Cancer Incidence Report, SCR, 1999-2000 and 2007). The true incidence, particularly the incidence of different types of NHL, is not known because of under reporting and lack of details.

NHL frequently has extranodal involvement and there are geographical differences in the incidence of extranodal NHL. Primary extranodal presentation of NHL has been reported to be in 15-25% of NHL patients in the United States and 30-42% in parts of the Europe (Freeman et al, 1972; Banfi et al, 1968; Gurney et al, 2002; d'Amore et al, 1991; Muller et al, 2005). Although there are numerous reports dealing with extranodal NHL originating in almost every organ of the body, the literature on primary extranodal lymphoma as a group is limited. Extranodal NHL may pose significant challenges in routine lymphoma diagnosis and treatment, in part due to lack of suspicion at presentation. In addition to the variation in the incidence, there may be regional and geographical differences in the response to treatment, prognosis and survival for various types of lymphomas. Furthermore, the prognosis of primary extranodal lymphomas may be different from the NHLs with isolated nodal disease (Moller et al., 2004; Al Shemmari et al., 2008). In view of this, there is a need for further studies to elaborate on these issues for a disease that is heterogeneous and appears to be on the rise. In this paper we present our observations of clinicopathological pattern in a cohort of patients, focusing on differences from other ethnic and racial groups.

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Materials and Methods

All adult patients (age 14 years or older) diagnosed to have NHL in four tertiary care hospitals in Riyadh, Saudi Arabia, over a five year period (1st July 1994 to 31st June 1999) were included in the study. Patients presented locally or were referred from different parts of the country and managed in four different hospitals in Riyadh. A total of 855 adult patients with NHL presented during this period and were included in the study. Further information about the patients was obtained from the individual patient's notes and computer records at the treating centers. This study cohort of 855 patients was followed until Dec 2003. Patients were then grouped into nodal and primary extranodal groups. The clinico-pathological aspects of the patients with extranodal NHL are presented here.

Data were analyzed using statistical software SPSS (version 14). Results are expressed as mean ± standard deviation, absolute numbers and percentages. Student's t-test was used to study the association between different stages of NHL and LDH level. A p-value of ≤ 0.05 was considered significant.

The definition of primary extranodal lymphoma remains somewhat controversial especially in patients where both nodal and extranodal sites are involved and there are different proposals defining this disease (Freeman et al., 1972; d'Amore et al., 1991; Krol et al., 2003). We adopted the proposal by Krol et al who suggested to use a liberal definition of primary extranodal NHL that includes all patients who present with NHL that apparently originated at an extranodal site, even in the presence of disseminated disease, as long as the extranodal component was clinically dominant (Krol et al., 2003). Clinical stage was defined according to the Ann Arbor classification (Carbone et al., 1971). Disseminated disease was defined to be similar to stage IV-NHL but with a clinical course of single organ predominance. A separate staging system has been proposed for GI-NHL which appears to be clinically more relevant to the outcome of treatment (Rohatiner, 1994). For the ease of comparison, we used the Ann Arbor staging system for all cases. Histopathological reporting of lymphoma subtypes was according to the REAL classification. Some of the cases were reported according to the older nomenclature and an attempt was made, as far as possible, to reclassify these cases according to the REAL classification. HIV status of the patients was not known.

Results

Among the 855 cases of NHL registered during the study period, 354 (41.4%) patients were considered to have primary extranodal lymphoma. The mean age of

Table 1. Characteristics of 354 Patients with Extranodal NHL

Site of extranodal NHL	Number of patients	Patients (% of total)	M:F ratio	Mean age (yrs±SD)	Age distribution (% of total) 14-40	41-60	>60	Early stage disease (% of total)	Extensive disease (% of total)	DLBCL (% of total)
Total	354	100	1.5:1	55±18	26.5	43	42	55.9	44.0	71.9
Head & Neck sites	64	18	1.1:1	54±22	24.1	32.8	43.7	59.3	40.6	64.7
Tonsils	33	51.5	3.6:1	56±20	24.2	33.3	42.4	63.6	37.0	72
Salivary glands	8	12.5	1:1.6	54±14	12.5	50	37.5	75.0	25.0	71.4
Nasopharynx	10	15.6	1:1	63±18	20	20	60	50.0	50.0	50.0
Other sites	13	20.3	1.6:1	51±21	30.7	30.7	38.4	50.0	50.0	55.6
Skin (all)	51	14.4	3.6:1	49±16	37.2	15	27.4	66.7	33.3	40.0
Skin (excluding mycosis fungoides & T-cell NHL)	9	2.5	4.2:1	56±13	19	62	19	65.0	35.0	50.0
CNS	20	5.6	2.3:1	53±20	30	20	50	36.8	63.1	73.3
Bone	16	4.5	1.2:1	40±19	62.5	18.7	18.7	31.5	68.7	85.7
Thyroid	16	4.5	1:2.2	56±13	25	43.7	25	62.5	37.5	76.9
Soft Tissue	16	4.5	1:1.1	51±16	25	43.7	31.2	46.6	53.4	90.9
Lung	11	3.1	4.5:1	48±18	36.3	36.3	27.2	72.7	27.3	50
Liver	8	2.2	1:1	65±13	0	25	75	50.0	50.0	80
Spleen	6	1.7	5:1	48±21	66.6	0	33.4	40.0	60.0	--
Breast	5	1.4	1:4	52±22	40	20	40	80.0	20.0	75
Genitourinary tract	7	1.9	4:1	39±15	85.7	15.3	0	25.0	75.0	40
Pancreas	2	<1	--	52	0	--	0	100	0	100
Heart	1	<1	--	NA	--	--	--	NA	NA	100

* DLBCL: Diffuse large B-cell lymphoma, NA: not available

Table 2. Primary NHL of Gastrointestinal Tract (GIT): Summary of Incidence, Distribution and Characteristics

Site of GI-NHL	Number of patients	Patients (% of total)	M:F ratio	Mean age (yrs±SD)	Age distribution 14-40	41-60 (years)	>60	Early stage (% of total)	Extensive disease (% of total)	DLBCL (% of total)
Total	131	37	1.2:1	60±16	15.2	30.5	42	57.8	42.2	77.8
Stomach	107	81.6	1:1	62±14	11.2	59.8	28.9	60.6	39.3	83
Small intestine	18	13.7	2:1	54±22	33.3	38.8	27.7	47	53	54.6
Large intestine	6	4.5	All males	45±9	33.3	66.6	--	40	60	60

Table 3. Comparison of the Sites and Percentage of Patients in Each Category of Extranodal Lymphomas From Different Countries

Country	Canada[1]	Egypt[2]	Pakistan[3]	USA[4]	Denmark[5]	Saudi Arabia[6]
Total GI-NHL	24	21	37.5	37	30	37.0
Stomach	--	10	--	24	19	30.2
Small intestine	--	5	--	8	9	5.0
Large intestine	--	6	--	5	2	1.8
Head & Neck sites	32	20	15	21	4	18.0
Thyroid	6	<1	--	3	5	4.5
CNS	10	1	9	2	7	5.6
Lung/thorax	1	--	3.5	4	5	3.1
Soft tissue	5	--	--	9	3	4.5
Bone	4	11	11	5	9	4.5
Skin	4	4	--	8	4	14.4
Genitourinary tract	4	6	4	0	2	1.9

[1]Zucca (1997) et al, [2]Sutcliffe (1992) et al, [3]Abid (2005) et al, [4]Freeman (1972) et al, [5]D'Amore (1991) et al, [6]Present study

patients with extranodal NHL was 55±18 years. Most patients presented in the age range of 41-60 years. There was a predominance of younger population (age <60 years) in the NHL of bone, lung, thyroid, genitourinary tract and spleen. On the other hand, older population (age >60 years) predominated in the NHL of head and neck (particularly nasopharyngeal NHL), CNS and liver. As a whole male: female ratio was 1.5:1.0. Extranodal NHL at certain sites showed predilection for one or the other gender. Skin NHL was observed more commonly in males than in females. The ratio became higher when cases with mycosis fungoides were excluded (M: F; 4.2:1). M:F ratio was also higher for the NHL of the intestine, brain, lung, spleen, tonsil and genitourinary tract. NHL of the salivary glands, thyroid and breast was more common in females than males. Overall, more patients presented with an early stage (stage I & II) than advanced stage (stages III & IV) disease. However, there were more cases of advanced or extensive disease at presentation of the NHL of CNS, thyroid, lung, and liver. Patients' characteristics and the breakdown of patients according to the site of involvement, mean age and age distribution, M:F ratio, stage of the disease and number (percent) of diffuse large B-cell lymphoma cases in each category are shown in Table 1.

Patients' data were also analyzed for the distribution of histological patterns. Diffuse Large B-cell Lymphoma (DLBCL) was the most common histological type comprising approximately 72% of all extranodal lymphomas. Other histologic types observed included: edxtranodal marginal zone B-cell lymphoma (MALT lymphoma-low grade), lymphocytic lymphoma, follicular lymphoma, Burkitt's lymphoma, mycosis fungoides (9.1% of the total extranodal NHLs but comprising 65% of skin NHL), other T-cell variants or unclassifiable. In general, 90.5% patients had NHLs with an aggressive histology.

The mean LDH at presentation was 265.3 ± 131.2 U/L for extranodular NHL. Mean LDH levels differed somewhat with stage, being 233.8 U/L for stage I, 224.5 U/L for stage II, and 243.9 U/L for stage III. These differences did not reach statistical significance. Mean LDH was significantly higher for stage IV (332.3±101 U/L, $p< 0.05$) as compared to stages I, II, & III.

NHL of the gastro-intestinal (GI) tract was the most common extranodal variety seen. In the GI tract, stomach was the most commonly involved site comprising more than 81% of the GI-NHL. Overall, there was a slight male preponderance in the GI-NHL (1.2:1) but it is noteworthy that all patients with NHL of the large intestine were males. Most cases of gastric NHL were of DLBCL type (82.8%), while the remaining cases included MALT lymphoma, Ki1+ NHL, plasmacytic or Burkitt's lymphoma. Average age at presentation was 60±16 years. Majority of the patients in the GI-NHL group (57.8%) presented with an early stage disease (stage I & II), but 60% of patients with NHL of the large intestine had an advanced disease at presentation. Furthermore, in contrast to the gastric NHL, DLBCL was found in approximately half of the patients with small and large intestine NHL.

Primary cutaneous lymphoma was observed in 51 (14.4%) patients with extranodal NHL. It was more common in males (M:F; 3.6:1) and mean age at presentation was 49±16 years. Some patients (17.4%) with skin lymphoma had NHL types other than mycosis fungoides or T-cell lymphoma and most of these patients (85%) had the DLBCL histology. Majority of these patients (85%) presented with primary involvement of the trunk followed by the lower limbs (12%).

Discussion

This is the first report of clinicopathological pattern of extranodal NHL in a large cohort of adult patients from Saudi Arabia. There are only few descriptive reports of extranodal NHL as a group although primary extranodal lymphomas constitute a significant proportion of all NHLs. There are regional variations in the incidence of primary extranodal NHL and the incidence of extranodal NHL has been reported to be around 15-50%, with the notable exceptions of peripheral T-NHLs, showing extranodal manifestation in 82% of the cases and almost always involving the skin (Freeman et al., 1972; Gurney et al., 2002; D'Amore et al., 1991; Muller et al., 2005). Our study found the prevalence of extranodal lymphoma to be 41.4% of all NHLs. This is similar to the prevalence reported from the neighboring Kuwait (45-50% of all NHL) indicating the possible role of common genetic and environmental factors in the etiology of extranodal NHL in this region (Temmim et al., 2004; Al Shemmari et al., 2008). This incidence is higher than reported from the USA and some of the western countries (Freeman et al., 1972; D'Amore et al., 1991; Gurney et al., 2002; Muller et al., 2005). Extranodal NHL is uncommon in some parts of the world (Rusinowska et al., 1996), while a strikingly high rate (58.9%) of extranodal NHL was reported from Pakistan (Abid et al, 2005). This variation in incidence prompts the need for further studies to elaborate on the role of any contributing genetic or environmental risk factors.

Table 3 compares the incidence of various site-specific NHL in different geographical regions. The gastrointestinal tract is the predominant site of extranodal NHL (Herrmann et al., 1980; Paryani et al., 1983; D'Amore et al., 1994) accounting for almost one third of all primary extranodal NHL but this incidence may vary in different areas (Ducreux et al., 1998; Papaxoinis et al., 2006). Within the gastrointestinal tract (GIT), primary gastric NHL is by far the commonest, comprising 50-60% of all GIT-NHL, and therefore, considered the most common site of extranodal lymphoma involvement (Zucca et al., 1997). Our study revealed a higher proportion of primary GI-NHL (42.4%) with primary gastric NHL comprising 81% of these cases. This rate is also higher than reported from some other countries like Canada and Egypt (Sutcliffe, 1992; Ahmed et al, 1997). The high prevalence of gastric NHL likely reflects the influence of environmental factors and may be related to the high prevalence of Helicobacter pylori infection in Saudi Arabia (al-Moagel et al, 1990; Marie et al, 2008).

Our study is comparable to a previous report from Saudi Arabia that patients with intestinal NHL present at an earlier age than gastric NHL patients, and they have more extensive disease at diagnosis (Ibrahim et al., 2001). The incidence of intestinal NHL appears to be lower in Saudi Arabia when compared to reports from some of the other regions (Herrmann et al., 1980; Morton et al., 1993). Genetic susceptibility, dietary habits, infections, immunosuppressive therapy and other environmental factors may contribute to these differences (Levine et al., 1992; Muller et al., 2005; Abid et al., 2005).

DLBCL is the most common type of non-Hodgkin's lymphoma in the Western countries, comprising 30-40% of all NHL cases (Morton et al., 1993; Muller et al., 2005). The prevalence of this type of NHL is much higher in this cohort and overall around 70% of our patients presented with DLBCL. It is noteworthy that in the present study DLBCL was the predominant histological variant in patients with NHL of the stomach, CNS, bone, thyroid and soft tissues, involving around 80% of the cases. Again, there are regional differences. One study from Greece, for example, reported 44.5% of DLBCL cases in gastric NHL, much lower than observed (78%) in our patients (Ducreux et al, 1998). The proportion of DLBCL was 71% in the extranodal NHL cases reported from Kuwait, similar to our results (AlShemmari et al, 2008). Abid et al reported a very high proportion of DLBCL (76.4%) in a large series of NHL patients from southern Pakistan (Abid et al., 2005). This high incidence of aggressive NHL at these sites may lead to poor outcome of treatment and this observation has important implications for therapy and prognosis.

A different classification system has been proposed for cutaneous lymphomas which has clinical implications (Levine et al, 1992). Lymphomas of the skin are more often of T-cell type, with Sezary syndrome and mycosis fungoides comprising around 65% of the cases (Armitage et al., 1997; Williemze et al., 2005; Diamandidou et al., 1996). Our study shows that these variants constitute up to 80% of skin lymphomas. Excluding these variants, skin NHL constituted 2.5% of all extranodal NHLs which is lower than reported in other studies (Table 3). It is important to note that skin lymphomas involve predominantly the males, present mostly at an earlier stage of disease, and aggressive histology is present in majority of the patients.

Primary NHL of the bone comprises 3% -7% of all extranodal NHL with a peak incidence in the fifth decade, a slight male preponderance and the disease originates from the long bones of lower limbs in most of the patients (Burg et al, 1995; Baar et al, 1999; De Camargo et al, 2002). The incidence of bone NHL in this cohort (5.6%) is comparable to other reports. The mean age at presentation was 38 years in our patients, younger than reported in other studies. DLBCL was the most common histologic variant observed in 85% of cases.

The incidence of thyroid NHL is almost twice as high in our study population (2% of extranodal NHL) as compared to reported elsewhere (Jacobs et al, 1985). Thyroid NHL appears to affect elderly females more commonly (Tsang et al, 1993) and this pattern is also seen in our population. In contrast to other studies, more patients presented with an early stage disease in our study. In addition, there was a higher prevalence of aggressive histology in our patients and this finding has implications for planned treatment (Doria et al, 1994).

In conclusion, extranodal NHL is common in Saudi Arabia and diffuse large B cell lymphoma is the most common histologic subtype. We found significant differences in the pattern of extranodal NHL in Saudi patients compared to those reported from other parts of the world. Further studies focused on the risk factors and treatment outcomes are needed to better understand the

biology of a disease common in this population.

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