

## A STUDY OF THE MORPHOLOGICAL PATTERNS OF EXTRANODAL NON-HODGKIN LYMPHOMA IN PAKISTANI AND SAUDI POPULATIONS

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### ABSTRACT

*Background: The incidence of extranodal non-Hodgkin lymphoma (EN – NHL) is increasing particularly among the populations of South Asia and Middle East. On the whole 25 – 40% of NHL arise in the sites other than lymph nodes.*

*Objectives: This study was designed to assess the pathological patterns and the prevalence of EN-NHL in Pakistan and in Saudi Arabia.*

*Methods: A total of 106 and 42 cases, from one centre in Pakistan and Saudi Arabia respectively, were included during a five year period (1998 – 2003) with a detailed account of their demographic and clinical characteristics.*

*Results: We observed that most of the Pakistani and Saudi patients presented in the 5<sup>th</sup> – 7<sup>th</sup> decades with the mean age being 43.2 and 46 years and a male to female ratio of 1.07 : 1 and 1.7 : 1 respectively. Apart from a diverse pattern observed, diffuse large B cell lymphoma (57.5% and 63.4%) followed by MALT lymphoma (28.3% and 26.8%) were the commonest morphological subtypes of EN – NHL in both genders belonging to Pakistan and Saudi Arabia respectively. The tumours were found to be widespread, however, a predominant gastrointestinal tract (45% and 41.3%), in particular, gastric involvement was seen in (20.8% and 19.5%) Pakistani and Saudi patients respectively. However, predominant orbital involvement was seen exclusively in the latter.*

*Conclusion: EN – NHL is an emerging malignancy in Pakistan and Saudi Arabia. Apart from a slight variation, no significant divergence was observed in the histological patterns of the EN – NHL in both geographical areas.*

*Key words: Extranodal (EN), Non Hodgkin lymphoma (NHL), Pakistan, Saudi Arabia.*

### INTRODUCTION

Non – Hodgkin's lymphomas (NHL) mostly arise in the lymph nodes, however approximately 25 – 40% may arise in tissues other than the lymph nodes and therefore termed as extranodal non Hodgkin lymphomas (EN – NHL).<sup>1</sup> NHL is implicated especially in terms of differences in presentation, behaviour and survival between the nodal and extra-nodal lymphomas and therefore should be considered as distinct entities with differing aetiologies.<sup>2</sup> These form a diverse group of neoplasia exhibiting a multifaceted epidemiological data on the incidence, morphological subtypes and clinical behaviour.<sup>3</sup> It has been observed that during the last two decades the incidence of lymphoma has increased, and that of EN – NHL increased more rapidly than the nodal type<sup>4</sup> particularly in developing countries. In these countries combination of environmental, infectious and genetic factors affect the development of these disorders.<sup>5</sup> In earlier reports, the proportion of lymphomas at extra – nodal sites has ranged from about 20% to 50% in different European, Asian and Mi-

ddle Eastern countries. From these studies and as stated by the international population – based cancer incidence data, (WHO, 1990), the geographical patterns of incidence of EN – NHL as being between 25% and 35% in most countries. Among them the stomach, skin and small intestine being the most common extra-nodal sites. In general, the pattern of incidence rates for EN – NHL tends to reflect that of other lymphomas. The age incidence curve of each site – specific EN – NHL is similar to that of N – NHL. In countries where total lymphoma incidence is high the incidence of lymphomas at each extranodal site also tends to be relatively high.<sup>6</sup>

The incidence of EN – NHL is also increasing among patients of South – East Asia and Arabic descents in Middle East<sup>7</sup>. In a study at Karachi, NHL has been reported as the sixth most common malignancy in both genders with an incidence of 9.6/100,000 in males and 7.2/100,000 in females. It has been reported as the most common cancer in Northern Pakistani males<sup>5</sup>. In the Middle East, NHL constitutes 60 – 75% of all cases of lymphomas as

suggested by others.<sup>8</sup> According to International Lymphoma Study Group (ILSG), in Kuwait, EN – NHL formed 53% of 206 cases of NHL<sup>13</sup> whereas in Kingdom of Saudi Arabia (KSA), a high frequency of EN-NHL with a high proportion affecting the gastrointestinal tract, particularly the stomach was reported.<sup>9</sup>

The different subtypes of EN – NHL have been recognised and widely studied worldwide either separately or as a group. Diffuse large B – cell lymphoma (DLBCL) is the most common EN-NHL. It is also the most common lymphoma encountered in the gastrointestinal tract and central nervous system, in addition eyes, paranasal sinuses, bone, testis, female genital tract, salivary glands, thyroid, the mediastinum, orbit, the oral cavity etc<sup>10</sup>. This is mainly a disease of older adults, with a median age in the seventh decade, but younger adults and children are occasionally affected. There is a slight overall male preponderance but this varies according to the anatomical sites.<sup>11</sup>

Mantle cell lymphoma (MCL) is a disease of older adults, with a male preponderance.<sup>15</sup> A minority of patients present with extranodal disease, most often involving the gastrointestinal tract and rarely presenting with involvement of other extranodal sites<sup>12</sup>. Follicular lymphoma (FL) is among the most common lymphomas in the West, patients are adults; women are more commonly affected than men.<sup>13</sup> Only a few cases present primarily with extranodal disease involving the gastrointestinal tract, the skin, the ocular adnexa and the breast.<sup>13,14</sup> Extranodal natural killer (NK) / T-cell lymphoma (previously known as polymorphic reticulosis or lethal midline granuloma) usually affects adults, however children are affected occasionally; males have a preponderance.<sup>14</sup> This lymphoma produces ulcerative, destructive lesions in extranodal sites most often in midline facial structures (nose and palate). It involves skin, testis, gastrointestinal tract, and soft tissue.<sup>15</sup> Lymphomas that arise in paranasal sinuses are almost always of DLBCL type, whereas most lymphomas that arise in the nasal cavity are extranodal NK / T – cell lymphomas.<sup>16</sup>

Most patients with extranodal marginal zone B – cell lymphoma (MZL) are older adults, with a median age being in the seventh decade in most series. Infrequently, young adults and, rarely, children and adolescents are affected. The most frequent site for the development of marginal zone lymphoma is the stomach while other common sites include Salivary glands, ocular adnexa, intestine, thyroid, lungs, skin, larynx, thymus, breast, liver, urinary bladder, urethra, trachea, and dura mater.<sup>17</sup>

Burkitt's lymphoma (BL) in its endemic variety, related to Epstein Barr Virus (EBV) infection, has a very high incidence in equatorial Africa, whereas the

sporadic disease in other regions of the world is much less common. In Africa, about half of all childhood cancers are endemic BL however the adults are involved less frequently. It characteristically has a high chance of involving the jawbone which is a distinctive feature being rare in the sporadic BL whereas the abdomen is involved in more than 90% of children.<sup>18</sup> Lymphoplasmacytic lymphoma (LPL) is a rare disease representing only 1.5% of all NHLs. Men are slightly more likely involved (53% vs. 47%) and the average age at diagnosis is 63 years.<sup>19</sup>

## MATERIALS AND METHODS

This descriptive study was carried out at the Pathology Departments of King Edward Medical University, Polytest Clinic and the Pathology lab of Lahore Medical and Dental College, Lahore in Pakistan and the Pathology laboratory of King Abdul Aziz Hospital and Oncology Center, Jeddah, KSA. A total of 106 and 42 cases respectively of EN – NHL comprising of both males and females were histologically diagnosed during a period of five years i.e (June 1998 – July 2003). The pathology departments in these centres receive surgical specimens from major parts of the city as well as from the related large geographical areas in the province including many rural locations. Quality control for diagnostic pathology was maintained through internal and external quality checks. All specimens for the present study were grossly examined, processed for making paraffin blocks and evaluated on Haematoxylin and Eosin (H&E) stained sections. The slides in each case were examined by at least two histopathologists. After confirmation of the diagnosis of EN – NHL, sections showing the primary tumours were grouped according to the World Health Organization Histological Classification of lymphoid neoplasms and the terminology of the International Working Formulation study group for NHL. The following subtypes were segregated in this study, diffuse large B cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), extranodal marginal zone B – cell lymphoma of MALT type (MALT – L), lymphoplasmacytic lymphoma (LPL) and marginal zone B – cell lymphoma (MZL).

Demographic variables recorded were the hospital patient registration number, date, name, age, sex, address, topography, morphology, and grading. The cases were categorized by tumour site, age and sex of the patients. The data obtained was analysed using SPSS version 17.0.

## RESULTS

A total of 147 biopsies from different subjects and from various extranodal sites were included in this study. Among them 106 cases were reported in

**Table 1:** Relationship of Age to Frequency of various NHLs.

Age Group (years)	Region	Tumour Types										Total n (%)
		DLBCL	MALT	FL	BL	TCL	MF	SLL	LPL	MC	NOS	
0 – 10	Pakistan	04	--	--	01	--	--	--	--	--	--	05 (4.7)
	S. Arab	02	01	--	--	--	--	01	--	--	--	04 (9.8)
11 – 20	Pakistan	02	03	--	02	02	--	--	--	--	--	09 (8.5)
	S. Arab	01	--	--	02	--	--	--	--	--	--	03 (7.3)
21 – 30	Pakistan	08	02	01	--	--	01	--	--	--	--	11 (10.4)
	S. Arab	--	02	--	--	--	--	--	--	--	--	02 (4.9)
31 – 40	Pakistan	06	03	--	--	01	--	--	--	--	--	10 (9.4)
	S. Arab	01	03	--	--	--	--	--	--	--	--	04 (9.8)
41 – 50	Pakistan	09	05	--	--	01	--	--	--	01	--	16 (15.1)
	S. Arab	07	--	--	--	--	--	--	--	--	--	07 (17.1)
51 – 60	Pakistan	09	07	01	--	--	--	--	--	--	--	17 (16.1)
	S. Arab	08	02	--	--	--	--	--	--	--	--	10 (24.4)
61 – 70	Pakistan	12	05	01	--	01	--	--	--	--	--	19 (17.9)
	S. Arab	07	02	--	--	--	--	01	--	--	--	10 (24.4)
71 – 80	Pakistan	04	02	--	--	--	--	--	--	--	01	07 (6.6)
	S. Arab	--	01	--	--	--	--	--	--	--	--	01 (2.4)
81 – 90	Pakistan	02	--	--	--	--	--	--	--	--	01	03 (2.8)
	S. Arab	--	--	--	--	--	--	--	--	--	--	0
Total	Pakistan	31	29	02	03	05	01	--	--	01	02	106
	S. Arab	26	11	--	02	--	--	02	--	--	--	41

**Table 1:** Distribution, as regards to age and various morphological types of EN – NHL in patients from Pakistan and Saudi Arabia respectively. Where DLBCL: diffuse large B cell lymphoma, MALT: mucosa associated lymphoid tissue lymphomas, FL : follicular lymphoma, BL : Burkitt's lymphoma, TCL : T cell lymphoma, MF: mycosis fungoides, SLL : small lymphocytic lymphoma, LPL : lymphoplasmacytic lymphoma, MC : mixed cell lymphoma, NOS : not otherwise specified.

Pakistan and 41 in KSA. As regards the sex, among 106 cases reported in Pakistan, 51.88% (n = 55) were males and 48.1% (n = 51) were females. On the other hand, of the 41 cases reported from Saudi Arabia, 63.4% (n = 26) were males and 36.59% (n = 15) were females. The male to female ratio was observed to be 1.07 : 1 and 1.7 : 1 in Pakistani and Saudi study groups respectively.

As regards the age, amongst 106 Pakistani and 41 Saudi cases, the age range was from < 10 years to 90 (mean : 43.2 ± SD) and <10 years to 80 years (mean: 46 ± SD) respectively. The age frequency (table 1), reflects a maximum number of patients i.e

17.9% (n = 21) and 24.4% (n = 10), being observed in the age groups of 61 – 70 and 51 – 60 years in Pakistani and Saudi study cases respectively. The sex – wise distribution of the morphological types of EN – NHL showed that among the 51 Pakistani and 26 Saudi male patients, the highest number of cases i.e 60.7% (n = 31) and 61.5% (n = 16) presented with DLBCL followed by MALT lymphoma in 31.3% (n = 16) and 23.1% (n = 06) groups respectively. The other tumours found in Pakistani males were TCL in 7.8% (n = 4), FL and BL in 3.9% (n = 2) each and MC and tumours of NOS type in 1.9% (n = 1) each. On the other hand, BL and SLL were the only other

common tumours seen in 7.7% (n = 2) cases each in Saudi males. Among the 51 Pakistani and 15 Saudi female patients, the maximum number of cases i.e 58.8% (n = 30) and 66.6% (n = 10) presented with DLBCL followed by MALT lymphoma in 29% (n = 14) and 33.3% (n = 05) cases respectively. No other tumour types were seen in Saudi females whereas 1.9% (n = 1) case each of TCL, FL, BL, MF, LPL and NOS tumours were seen in Pakistani females. This indicates that male preponderance was observed in both Pakistani and Saudi populations.

Among the 106 Pakistani patients, the maximum number (12%; n = 12) of cases presenting with DLBCL were in the age group of 61 – 70 years, followed by 7.2% (n = 07) cases with MALT lymphoma and 2% (n = 02) cases each of BL and TCL in the age group of 11 – 20 years. Similarly, among the 41 Saudi patients, the maximum number (19.5%; n = 08), of cases presenting with DLBCL were in the age group of 51 – 60 years, followed by 7.3% (n = 03) cases with MALT lymphoma in the age group of 31 – 40 years and 4.9% (n = 02) cases with BL in the age group of 11 – 20 years (Table 1).

The EN – NHL both in Pakistan and KSA had a widespread distribution in a variety of organs and tissues. Among the 106 Pakistani and 41 Saudi cases, stomach was the commonest site of involvement in 20.8% (n = 22) and 19.5% (n = 08) cases respectively. This was followed, in Pakistani patients, by small intestine in 12.2% (n = 13), nasopharynx in 11.3% (n = 12), colorectum in 8.3% (n = 9), salivary glands in 6.6% (n = 7), bone in 5.6% (n = 6), duodenum in 3.7% (n = 4), nose, skin, thyroid in 2.8% (n = 3) each, liver, lung chest wall, ovary, breast and paraspinal area in 1.8% (n = 2) each and oesophagus, omentum, pelvic peritoneum, oropharynx, soft palate, pyriform sinus, bronchus, cervix, spinal cord, soft tissue, orbit and frontal lobe of brain in 0.9% (n = 1) case each. On the other hand, in Saudi cases, following stomach, colorectum in 12.1% (n = 5), orbit in 10.4% (n = 05), small intestine in 9.7% (n = 04), salivary glands, bone in 7.3% (n = 03), nasopharynx, soft palate, thyroid in 4.8% (n = 02) each, and oral cavity (gums), liver, tonsil, ovary, testis, bone marrow, spine, supraorbital and extradural space in 2.4% (n = 01) each were the least common sites of involvement. Among the 106 Pakistani and 41 Saudi biopsies, gastrointestinal EN – NHL formed 45% and 41.3% respectively.

## DISCUSSION

EN – NHL is not uncommon; its natural history and treatment are clearly characterized in the literature however data in relation to survival and prognostical factors of EN – NHL is scarce in this part of the world.<sup>20</sup> This study focused on indicating, if any, geographical variation in the incidence, clinicopa-

thological features and morphological subtypes of EN – NHL exist between Pakistan and KSA study population groups. As reported by Antonia, available epidemiological data from various parts of Asia revealed a higher incidence of an aggressive variety of EN – NHL<sup>21</sup> but the WHO report, in the year 1999, depicts much less variation, ranging from 22 to 25% of all lymphomas in the USA to 33% in Denmark and 34% in Middle East. Only France (42%) and Kuwait (52%) have particularly high relative frequencies at extra – nodal sites. In general, stomach and skin, followed by small intestine were reported to be the commonest extranodal sites.<sup>6</sup>

Though depicted by previous literature, EN – NHL is more common in males however there is a significant difference in the male to female ratio in various series. Data from developed countries report a male to female ratio of 1.4 : 1 while from developing countries the ratio ranges from 4.5 to 3.1.<sup>22,23</sup> Our findings revealed an equal gender distribution of EN–NHL in Pakistani patients whereas male preponderance was seen in KSA. This is similar to the findings of Morad and Kurana<sup>9</sup> who reported the M : F ratio as 1.95 : 1 in a study at Abha, KSA but a male dominant pattern was reported by Lal et al.,<sup>2</sup> Kanwal<sup>24</sup> and Zeba et al.<sup>25</sup> in four large series of EN-NHL showed almost 2.2 – 2.7 : 1 M : F ratio. Age distribution showed a similar picture in both countries with most of the cases presenting in the 5<sup>th</sup> to 7<sup>th</sup> decades. The mean age of the patients was approximated in both countries and corresponded well with the other studies.<sup>2,9,24-26</sup>

Amongst the histological subtypes, DLBCL followed by MALT lymphoma were the commonest tumours in both sexes in Pakistan as well as KSA. These findings closely matched with other Saudi reports from Zeenath<sup>26</sup> and Morad<sup>9</sup> and also with the above mentioned Pakistani studies except Kanwal<sup>24</sup> who reported MALT lymphoma and SLL as the commonest tumours among her study group where the latter, in fact, was seen in only Saudi males in the present study.

Analogous to the findings of Lal et al.<sup>2</sup> (44%) and the data from Karachi Cancer Registry<sup>25</sup> (54.1%) in Pakistan and Morad<sup>9</sup> (52.8%), Zeenath<sup>26</sup> (56.6%) and Ibrahim et al.<sup>27</sup> (43.1%) from KSA, gastrointestinal tract (GIT) was the commonest system involved by EN – NHL in both sexes in Pakistan (48.2%) and KSA (34%). Among the GIT, stomach was the most frequently involved site of EN-NHL in both countries, consequent with the previous Saudi reports.<sup>9,16,27</sup> On the other hand, Kanwal and Zeba et al. reported salivary glands and bone marrow as the most commonly involved organs followed by GIT and liver respectively.<sup>24,25</sup> Orbit was also another frequent site of EN – NHL in the Saudi cases only. Rest of the organs and tissues involved were almost

similar to that of other relevant studies reported.<sup>2,5,9,24-27</sup>

The incidence of malignant neoplasms reported from major countries of Middle East indicated an increased frequency of EN – NHL, particularly involving GIT i.e gastric lymphoma is more frequent than the intestinal and when compared with the western reports, the patients observed in this region are about 10 years younger.<sup>28</sup> Investigators from Kuwait, Bahrain and Turkey reported an incidence of EN – NHL to be 45%, 41.7% and 46% with the mean age ranging from 38 – 45.5 years and the male to female ratio from 1.48 : 1 to 2.1 : 1 in various series. Morphologically, DLBCL, MALT lymphoma and SLL were the commonest types and GIT was the most frequently involved extra-nodal site in which stomach followed by intestine in all reports.<sup>7,10,28,29</sup>

As far as the data from the West is concerned, in a USA based study, NHL ranks fifth in incidence and approximately 27% of all NHL cases in the year 2000 were extranodal<sup>1</sup> whereas Comprehensive Cancer Centre West (CCCW) NHL registry reports 25 – 40% of all NHL patients presenting with a primary EN – NHL. The median age of the reported western population was 67 years and for most morphological groups, ranged between 21% and 33%. Almost half of all EN – NHL cases were DLBCL followed by FL, MALT lymphoma, LPL, BL, MCL and Peripheral TCL. Gastrointestinal tract, predominantly stomach and small intestine, head and neck, soft tissue, thyroid, and testis were the commonest sites.<sup>30</sup>

As a result of this study it is **concluded** that EN-NHL is seen as an emerging problem in the region including the subcontinent and KSA. It is seen most frequently in the gastrointestinal tract particularly the stomach. Among the morphological types DLBCL and MALT lymphomas form the commonest NHL in that order. As regards age, most cases in our study groups occurred between 51 and 70 years. Sexwise, the males dominated in Saudi group, whereas Pakistani group the sexes were divided equally.

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#### CONFLICT OF INTEREST

None to declare.

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