

Primary Extranodal Non-Hodgkin Lymphoma: A 2-Year Retrospective Analysis from a Tertiary Care Centre in Rajasthan

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ABSTRACT

Introduction: Primary extranodal lymphoma (pENL) refers to group of disorders arising from tissues other than lymph nodes and even from sites, which normally do not contain lymphoid tissue. The incidence of extra nodal non Hodgkin lymphoma (ENL) is rising throughout the world. However, data regarding ENL as a group is limited. This study was undertaken to ascertain the prevalence, anatomical distribution, and histological subtypes of extranodal non-Hodgkin lymphoma (NHL) from a tertiary care institute in Rajasthan.

Materials and Methods: This was a cross-sectional study conducted in the Department of Pathology over a period of 2-years. Detailed clinical history, routine complete blood count, microbiological status was obtained from the medical records. Hematoxylin and eosin slides were reviewed and immunohistochemistry was performed using a panel of antibodies depending on the morphology. All cases were classified based upon morphologic and immunophenotypic criteria according to World Health Organization 2008 classification.

Results: Primary extranodal NHL constituting 54.7% (70/128) of all NHL and the majority of patients were from higher age group with peak incidence seen in fifth and sixth decade of life. In the pediatric population, the most common site was GI tract (45.5%) followed by skin (18.2) and the most common morphology was diffuse large B-cell lymphoma (54.5%).

Similarly in the adult population CNS was the most common site constituting 20.3%, followed by head and neck (18.6%) and diffuse large B-cell lymphoma was the most common morphological subtype comprising 64.4% of all adult extranodal lymphomas.

Conclusion: Although the reported incidence of pENL is low in India compared to other parts of the world, the possibility of pENL should always be kept in mind even though it arises in an extranodal site.

Keywords: Extranodal, non-Hodgkin lymphoma, Primary.

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a group of lymphoproliferative, malignant disorders arising in lymph nodes with heterogeneous, histological, and clinical characteristics.¹ At least one-quarter of NHL arise from tissues other than lymph nodes and even from sites, which normally do not contain lymphoid tissue. These forms are referred to as primary extranodal lymphomas^{2,3} (pENL). Extranodal lymphoma diagnosis is a frequent challenge to the pathologists, due to their morphological mimics, molecular alteration and clinical presentations.

Over the past twenty years lymphomas arising in the extra nodal sites have shown a rapid increase in incidence especially in central nervous system, gastrointestinal tract (GIT) and the skin.⁴ This may be attributed to immunosuppression due to AIDS or immunosuppressive treatments, infections such as *Helicobacter pylori*, *Chlamydia psittaci*, *Borrelia burgdorferi*, and *Campylobacter jejuni*, autoimmune disorders and environmental factors.⁴ The types of lymphoma encountered vary widely from one extranodal site to another. Extranodal lymphoma is further classified as primary and secondary. Secondary indicating that the lymphoma first presented in the nodes⁵ and subsequently involved the extranodal sites.

In addition to the variation in the incidence, there may be regional and geographical differences in response to treatment, prognosis and survival for various types of lymphomas. Although there are numerous reports dealing with extranodal NHL originating in almost every organ of the body, the literature on pENL as a group is limited.

Many studies on pENL incidence patterns or distribution were reported all over the world. However, research on distribution of pENL in the state of Rajasthan was still limited, case number was also small. This study was undertaken to ascertain the prevalence, anatomic distribution, histological subtypes of extranodal NHL and to compare the data of ours with those reported in literature from a tertiary care institute in Rajasthan.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pathology over a period of 2-years. During this period, 128 NHL were diagnosed. Of them, 70 cases were pENLs. Tissue was processed routinely in 10% formalin and 5 μ paraffin sections were stained with hamatoxylin and eosin. Immunohistochemistry (IHC) was performed using a panel of antibodies depending on the

morphology. Immunohistochemical analyses were performed manually on the paraffin embedded tissue sections by using a panel of monoclonal antibodies. Antigen retrieval was done by pretreatment of paraffin sections by heating in a Pascal pressure cooker in 0.01 M citrate buffer (pH6.0). The panel of antibodies used for IHC includes leukocyte common antigen (LCA), CD3, CD4, CD5, CD8, CD19, CD20, CD23, CD10, CD15, CD30, CD99, CD56, Bcl2, Bcl6, MUM-1, BOB-1, PAX-5, Tdt, anaplastic lymphoma kinase-1 (ALK-1), cyclinD1, Ki67, epithelial membrane antigen (EMA) and pancytokeratin (panCK). Molecular diagnostic techniques such as cytogenetics/fluorescence in situ hybridization were not performed in any of the cases due to lack of facilities. Data pertaining to patients' demography, ethnicity, occupation, clinical presentation, immune status, routine complete blood count, and microbiological (HIV, EBV, H. pylori, HCV, and HBV) status were obtained from the medical records.

The definition of pENL remains somewhat controversial, especially in patients where both nodal and extranodal sites are involved, and there are different proposals defining this disease.⁶⁻⁸ We adopted the proposal by Krol et al. who used 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. Another problem concerns the debate about whether tonsil and Waldeyer's ring (WR) should be considered as nodal or extranodal lymphoma sites.⁹ In many respects, they could be considered of nodal origin, but they have historically been included among the extranodal types¹⁰⁻¹³ and therefore, we have included them as an extranodal site.

Primary nodal NHL with secondary extranodal involvement was excluded from the study.

As per Dawson criteria⁷, lymphoma is said to be primarily extranodal if

- 1) absence of palpable superficial lymph nodes on first physical examination;
- 2) absence of mediastinal lymphadenopathy detected on plain Chest X-ray;
- 3) dominant lesion at extranodal sites;
- 4) involvement of lymph nodes in the vicinity of the primary lesion; and
- 5) white blood cell (WBC) count within normal range.

All cases were classified based upon morphologic and immunophenotypic criteria according to World Health Organization (WHO) 2008 classification.¹⁴ Clinical stage was defined according to the Ann Arbor classification.¹⁵

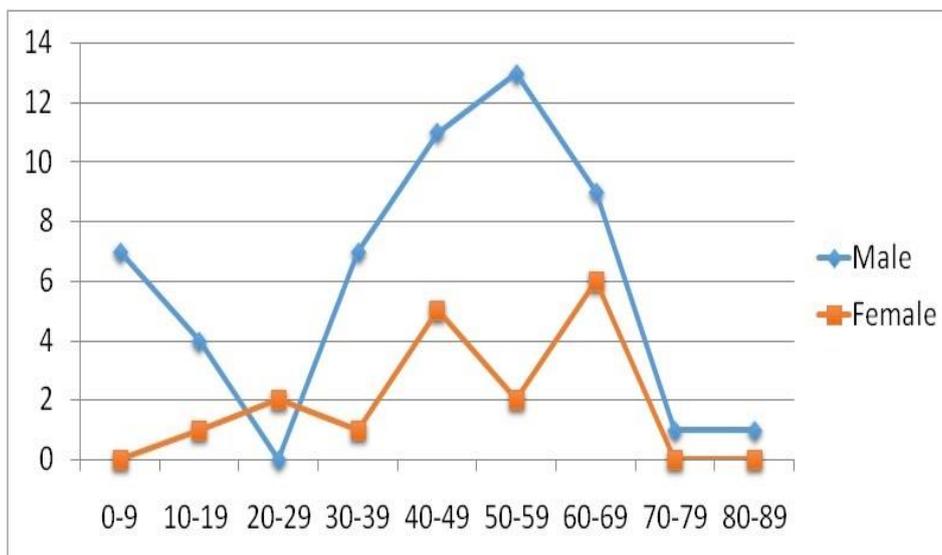


Fig 1: Age and sex distribution of primary extranodal lymphomas

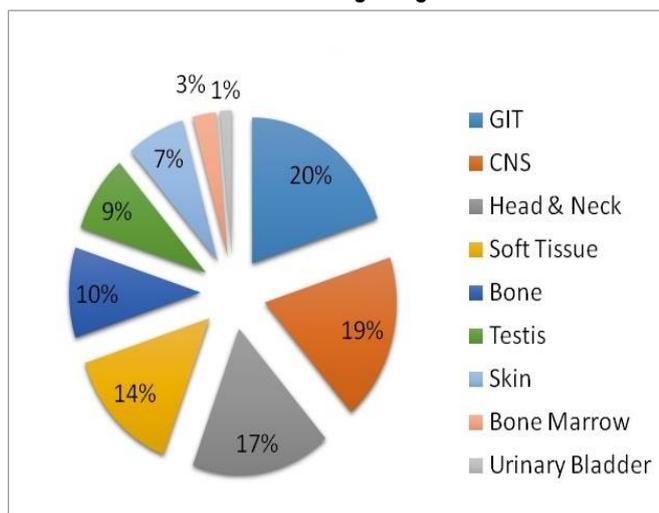


Fig 2: Anatomic Distribution in primary extranodal non-Hodgkin lymphomas

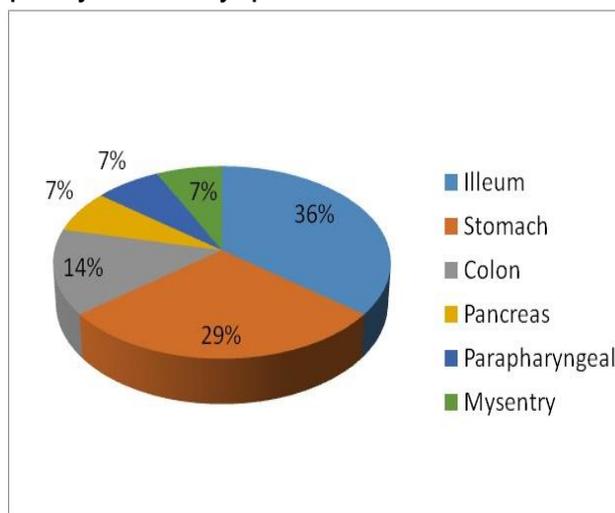


Fig 3: Site distribution of primary extranodal GIT lymphomas

RESULTS

Primary extranodal NHL constituting 54.7% (70/128) of all NHL diagnosed over a period of 2-years were included in the study. Our study included 53 males and 17 females, with a Male: Female ratio of 3:1 approximately. Majority of our patients were from higher age group with peak incidence seen in fifth and sixth decade of life (age range 4-89 years) [Fig 1]. The different sites that were involved in pENL is shown in Fig 2. Classifying according to the WHO 2008 classification, DLBCL was the commonest histological subtype comprising 62.9% of all extra nodal lymphomas followed by plasmacytic neoplasm 12.9%, small lymphocytic lymphoma (SLL) 10%, anaplastic large cell lymphoma (ALCL) and burkitt's lymphoma (BL) both having 4.3% each, lymphoblastic lymphoma (LL) 2.9%, peripheral T-cell lymphoma NOS (PTCL-NOS) and maltoma both 1.4% each. [Table 1]. In adult population CNS was the most common site of pENL in our study constituting 20.3%. Head & neck was the second most common site with 18.6% cases, GIT and soft tissue with 15.3%

each, bone 11.9%, testis 8.5% and skin 5%. Bone marrow and Urinary bladder were the least common sites being involved comprising 3.4% and 1.7% respectively. B-cell lymphomas were seen in 93.5% of cases where as T-cell was seen in 6.5% of cases. Nasal cavity was the most common site in the head and neck region (25%) followed by submandibular gland and tonsil (16.7%) each. In the GIT, illeum was the most commonly involved site comprising 35.7% followed by the stomach at 28.6% and colon with 14.3%. [Fig 3]

In the pediatric population there were 11 cases. The age ranged from 4 to 17 years with Male: Female ratio of 10:1. Sites involved were GI tract in 5 cases, skin in 2 cases and; 1 case each of soft tissue, head & neck, CNS and testis. Histologically, there were 6 cases of diffuse large B-cell lymphoma (DLBCL), 3 cases of Burkitt lymphoma (BL) and 1 case each of lymphoblastic lymphoma (LL) and anaplastic large cell lymphoma ALK+ (ALCL ALK+).

Table 1: Types of non-Hodgkin lymphoma seen at extra nodal sites

Site	DLBCL	PBL	SLL	ALCL	BL	LL	PTCL-NOS	Maltoma	TOTAL
GIT	13				1				14
CNS	6	4	1	1			1		13
Soft Tissue	8	1	1						10
Head & Neck	6	1	3		1			1	12
Bone	2	3	1			1			7
Skin	2			2	1				5
Testis	5					1			6
Bone Marrow	1		1						2
Urinary Bladder	1								1
TOTAL	44	9	7	3	3	2	1	1	70

GIT: Gastrointestinal tract; CNS: Central Nervous System; DLBCL: Diffuse large B-cell Lymphoma; PBL: Plasmablastic Lymphoma; SLL: Small Lymphocytic Lymphoma; ALCL: Anaplastic large cell Lymphoma; BL: Burkitt's Lymphoma; LL: Lymphoblastic Lymphoma; PTCL-NOS : Peripheral T cell Lymphoma, not otherwise specified;

Table 2: pENL- Comparison with other studies

Study	NHL	ENL(%)	Common Sites Involved (%)	Common Histological subtype
Jin-Man Kim et al.^[16] 2011 Korea	3807	2650 (69.6)	GIT (29) WR (09)	DLBCL MALT ENKTCL
Yang et al.^[17] 2011 China	5549	2986 (53.5)	WR (23.7) GIT (22.3) NPNS (20.4) Skin (11.3)	DLBCL ENKTCL MALT
Fujita et al.^[18] 2009 Japan	847	395 (46.6)	GIT (30.4) WR (17.8) Orbit (7)	DLBCL MALT
Singh et al. ^[19] 2003 Northern India	241	106 (44)	Head and Neck (50.9) GIT (27.4)	DLBCL
Padhi et al.^[20] 2012 Southern India	308	68 (22)	Brain (29.5) GIT (25) NPNS (11.8)	DLBCL MALT
Mishra et al.^[31] 2013 Southern India	300	68 (22.6)	Head & Neck (37) GIT (29)	DLBCL PTCL MALT
Present Study 2016 North- Western India	128	70 (54.7)	GIT (20) CNS (19) Head & Neck (17)	DLBCL

GIT: Gastrointestinal tract; WR: Waldeyer's ring; DLBCL: Diffuse large B-cell lymphoma; MALT: Mucosa associated lymphoid tissue; NPNS: Nose, nasopharynx and paranasal sinus; PTCL: Peripheral T-cell lymphoma; ENKTCL: Extranodal nasal-type NK/T-cell lymphoma; NK: Natural killer; pENL: Primary Extranodal lymphoma

DISCUSSION

Primary extra nodal lymphomas are a heterogeneous group of tumors because of its difference in epidemiology and etiology in different areas around the world. The frequency of extranodal NHL varies in different parts of the world. In countries where total lymphoma incidence is high the incidence of lymphomas at each extranodal site also tends to be high. Studies from Western countries have reported the occurrence of extranodal NHL as 24-48% of all NHL^{2,3,8,21} in contrast to Asian studies (Pakistan [42%], Kuwait [45%], Japan [46.6%], Korea [55%], Thailand [58.7%], and China [44.9-61.4%]),^{18,22-25} Compared to these data from other Asian countries, the prevalence in our series (54.7%) is more or less equivalent.

Table 2 compares the incidence of various site specific extra nodal Hodgkin lymphoma in different geographical regions. The GIT is the predominant site of extranodal NHL accounting for almost one-third of all primary extranodal NHL, but this incidence may vary in different areas. Within the GIT, primary gastric NHL is by far the most common of all GIT-NHL, and therefore, considered the most common site of extranodal lymphoma involvement in Korea¹⁶ and India.²⁶ However, head and neck region including WR have been reported to be the most common sites of origin of pENL in various studies from China¹⁷ and Taiwan.²⁷

In India, the incidence of pENL and the sites varies widely. A pioneer study from Northern India by Singh et al.¹⁹ showed extranodal lymphomas constitute 44% with the most common site being the head and neck, whereas a study conducted by Padhi et al.²⁰ from Southern India showed extranodal lymphomas constituted 22% and the most common site being the central nervous system. Western India shows incidence of 28% and GIT being the most common site that is affected. Our study showed incidence of 54.7% with GIT being the most common site of pENL. It is difficult to explain such diversities. These regional variation could again be attributed to differences in genetic and geographical factors, and more importantly these are all hospital based studies and hence not truly representative of population demographic profile.

In accordance to the literature, Diffuse large B-cell lymphoma (62.9%) was the most common histological subtype followed by Plasmacytic neoplasm (12.9%) and small lymphocytic lymphoma (10%) in the extranodal site. Follicular lymphomas were conspicuously absent in the extranodal sites, possibly as suggested by Biagi and Seymour,²⁸ that geographic variation and molecular expression profiling in follicular lymphomas could be a possible explanation.

Non-Hodgkin lymphoma of the GIT was one of the most common site to be involved in our study, ileum being the commonest site. DLBCL was the most common histological subtype. We also had one case each of rare pancreatic mass lymphoma and bladder mass lymphoma and both were of DLBCL subtype.

Primary CNS lymphomas account for <2% of extra nodal lymphomas, but the incidence is increasing in immunocompromised and immunodeficient hosts.^[29] Primary central nervous system lymphoma (PCNL) is defined as lymphoma arising in and confined to the cranial-spinal axis (brain, eye, leptomeninges and spinal cord). Formerly a rare tumour, PCNL has shown increased incidence both in immunocompromised (congenital, acquired or iatrogenic) high-risk groups and in the general population³. Our study showed an

incidence of 18.6% of primary CNS lymphomas. Testicular lymphoma is common beyond the age of 60-year, is usually bilateral, and the predominant histological type is DLBCL.³⁰ However, we have some interesting findings regarding testicular lymphomas in our study. We had four cases of testicular lymphomas below the age of 50-year of which in two cases the patient's age was <30 years and the histological subtypes were DLBCL in three cases, and one case showed lymphoblastic lymphoma (LL).

CONCLUSION

Primary extranodal lymphomas constitute a diverse group of hematolymphoid malignancies. The incidence of pENL is low in India compared to data from other parts of the world. Gastrointestinal tract and central nervous system were the two most common extra nodal sites observed. Compared to published series, no difference was noted in regard to gender predilection and morphology. The diagnosis is a frequent challenge to the pathologists, due to their morphological mimics, and varied clinical presentations. Therefore, the possibility of pENL should be kept in mind even though it arises in an extranodal site.³¹ Being mostly an epidemiological and morphological study, data pertaining to the detail therapeutic outcome are lacking. Lack of comparison with pediatric group (due to very less number) was another drawback of our study. However, we do believe that more in depth studies of similar kind, highlighting the genetic profile of lymphomas, should be carried out from time to time in order to understand the biology of this group of tumors.

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