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Original Article

Histopathological spectrum of primary extranodal non hodgkin's lymphomas in kashmir valley A 5 years study

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ABSTRACT

Background and Aim: The incidence of extra nodal non Hodgkin lymphoma (ENL) is rising throughout the world. However, data regarding ENL as a group is limited. The aim was to study the epidemiological and histomorphological trends of primary ENL (pENL) in Kashmir valley . Material and Methods: The biopsy materials from ninty six patients with pENL (64 male, 32 female, M:F= 2:1), diagnosed over a five year period (2008-2013), were analysed and pathologically reclassified according to the World Health Organization (WHO) classification, 2008 criteria. Results: Primary extra nodal non Hodgkin lymphomas constituted 24.0% (96/400) of all non Hodgkin lymphomas (NHL). The mean age at presentation for pENL and primary nodal NHL was 44.5 years and 58 years, respectively with a male predilection (M: F=2:1). Gastrointestinal tract (GIT) constituted the most common extranodal site (60/96, 62.5%) followed by Waldayer's ring(28/96, 29.16%). Diffuse large B-cell lymphoma (DLBCL, not otherwise specified), extranodal marginal lymphoma of mucosa associated lymphoid tissue (MALT) type, and B cell NHL unclassified (U) were the three most common histological types observed. T-cell phenotype was rarely noted (4%). Follicular lymphomas and anaplastic large cell lymphoma, seen among nodal NHL, were absent at extra nodal sites. Majority (60/96, 64%) of the patients with pENL were immunocompetent and 55% were in stage I-II with favorable prognosis. Conclusion: Gastrointestinal tract was the most common site of ENL, followed by waldayer's ring. Majority of pENL occurred in immunocompetent hosts with a favorable prognosis.

1. Introduction

Lymphomas are malignant disorders of cells residing in lymphoid tissues. A good percentage of non-Hodgkin's lymphomas (NHL) arise from tissues other than lymph nodes and even from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas (pENL).

At least one-fourth of the lymphomas are probably of extranodal origin [1,2,3,4]

Previous epidemiologic studies have shown remarkable differences in the distribution of lymphoma subtypes between Asian and western populations [5,6,7] . However, the possible reasons of geographic differences in the spectrum of lymphoma remain unknown, mainly because the etiology of lymphoma is largely unknown, even though some risk factors have been documented recently, including genetic factors, abnormality of immunity, individual susceptibilities, lifestyles, environmental exposures [8].

For many pENL, there are distinctive clinicopathological features, sometimes associated with an underlying immunodeficiency syndrome (HIV/AIDS, organ transplant), autoimmune disorders [Sjogren syndrome, systemic lupus erythematosus (SLE), scleroderma, inflammatory bowel disease (IBD), dermatomyositis, Hashimoto thyroiditis, rheumatoid arthritis], infection [Helicobacter pylori, Campylobacter jejuni, Borelia burgdorferi, Chlamydia psittaci, Epstein Barr virus (EBV), Human T-lymphotropic virus1 (HTLV- 1), Human herpes virus 8 (HHV-8), and Hepatitis C virus (HCV)] or a predilection to affect patients of certain ethnic origin [9,10,4]. HCV is considered as a virus with triple tissue tropism (hepatotropism, lymphotropism, and sialotropism) and this may explain the higher prevalence of sicca syndrome, cryoglobulinemia, and lymphoproliferative disorder (MALT lymphoma) in patients with chronic HCV infection [11] .

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Extra nodal NHLs have been reported to originate from almost every anatomic site of the body such as gastrointestinal tract (most common), head and neck (Waldeyer's ring, nose/paranasal sinses/nasopharynx, salivary glands, etc.), skin, central nervous system (CNS), bone, testis, thyroid, breast, orbit, and rarely adrenal, pancreas, and the genitourinary tract [12,13,14.15,16,17,18 ,19 ,8,20,21,22,23,24]

The definition of extranodal lymphoma, particularly in the presence of both nodal and extranodal disease, remains a controversial issue. Different criteria have been proposed by various authors in the past, to categorize these entities [25,26] . As per Dawson criteria, 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.

It has been observed that during the last two decades the incidence of NHL has increased, and that of pENL increased more rapidly than the nodal type [27]. This trend is seen particularly in

developing countries, more so in Middle East and Far East, with an increase in diffuse histological pattern over nodular, and more aggressive than indolent behavior [24,23] . The most dramatic change in trend, in last two decades, has been observed for primary CNS lymphoma (PCNL) which has increased four times as rapidly as other extranodal sites. This is partly due to AIDS pandemic, as well as improved diagnostic modalities, and it continues to rise in immunocompetent hosts of all ages and in both genders as well. [28,29,30].

Many studies on extranodal lymphoma incidence patterns or distributions were reported all over the world . However, research on distribution of extranodal Lymphoma in Kashmir valley was still limited, case number was also small. The purpose was to estimate the various aspects of pENL, from epidemiology to morphology, and to compare the data of ours with those reported in the literature.

MATERIAL AND METHODS

The present hospital based descriptive study was done within a period of five years (Jan 2008- Jan 2013) in the Department of Pathology GMC, SGR.

All newly diagnosed cases of NHL received in department were included in study. The total number of cases were 400. Paraffin embedded Haematoxylin and eosin (H and E) stained tissue sections were analysed by a group of histopathologist to reach at a morphological diagnosis. Immunohistochemical (IHC) analyses were performed on the paraffin embedded tissue sections by using a panel of monoclonal antibodies (Peroxidase-antiperoxidase method). Antigen retrieval was done by pre-treatment of paraffin sections by heating in a Pascal pressure cooker in 0.01 M citrate buffer (pH 6.0). The panel of antibodies used for IHC, based upon morphological analyses and anatomic sites, included pan cytokeratin (predilluted, PD), leukocyte common antigen (LCA, 1:75), CD3 (PD), CD20 (PD), CD5 (1:20), CD15 (PD), CD30 (PD), CD99 (PD), Bcl2 (1:200), anaplastic large cell lymphoma kinase-1 (ALK, PD), Cyclin D1(1:20), epithelial membrane antigen (EMA, 1:75), neuron specific enolase (NSE, 1:200), glial fibrillary acidic protein (GFAP, 1:150); all from Biogenex, and terminal deoxy transferase (TdT, PD, DAKO).

All cases were reviewed by minimum of two pathologists and reclassified based upon morphologic and immunophenotypic criteria according to World Health Organization 2008 classification [31]

Data pertaining to patients' demography, ethnicity, occupation, clinical presentation, prior drug history, immune status, routine complete blood count (CBC), microbiological (HIV, HCV, and Hepatitis B) status and biochemical parameters [serum total protein, serum albumin, lactate dehydrogenase (LDH), serum urea, creatinin, uric acid, bilirubin and liver enzymes] were obtained from the medical records. Clinical stage was defined according to the Ann Arbor classification [32]. Involvement of lymph nodes and were defined as nodal localisations, and the involvement of other organs was defined as extranodal . Patients were considered to be completely staged when adequate information was available on history, status of peripheral lymph nodes (physical examination), Waldeyer's ring (examination by an ENT specialist), mediastinal lymph nodes (chest X-ray), abdominal lymph nodes, liver and spleen [abdominal Computerized Tomogram (CT) scan] as well on peripheral blood and bone marrow (aspiration and trephine biopsy). The International Prognostic Index (IPI) was calculated according to the description by the International Non- Hodgkin's Prognostic Factors Project for patients with all required parameters present. Strict criteria proposed by Dawson et al were used to categorize the lymphoma as primary extranodal. Primary nodal NHL with secondary extranodal involvement and plasmacytomas were also excluded from the study. The clinico pathological profiles and pathology of pENL were compared with primary nodal NHL studied during the same study period (2008-2013).

All lymphomas, except PCNS, were managed with surgery and six cycles of chemotherapy [Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP) +/- Rituximab (R)], with or without radiotherapy.

Primary CNS lymphomas were managed with stereotactic biopsy and Methotrexate based chemotherapy, steroids, with or without radiotherapy.

RESULTS AND OBSERVATIONS

Primary extranodal NHL constituted 24% (96/400) of all NHL studied during this period. These included 64 males and 32 females (M: F=2:1) and peak incidence was during the 4th to 5th decade of life (age range 12-76 years, mean 44.5 years) (Figure 1). Majority of patients (62/96 64%) had no detectable underlying co-morbidities, whereas rheumatoid arthritis was seen in 10/96 10.41% patients . Twelve percent (12/96) of gastric MALT (mucosa associated lymphoid tissue) lymphomas had a prior history of H. pylori

Table 1 Comparison between Present Series of Primary Extranodal non Hodgkin Lymphoma with Published Series in Regard to Epidemiology, Pathology, and Biologic Behaviour.

Author place Year	NHLs (n)	Study Period Years	ENL (n) %	Anatomic site		Histopathology	
				Common	Uncommon	Nodal	Extranodal
Somanath[33] Padhi et al 2012 South India	308	5	68 (22)	Brain GIT NPNS	Bone, Testes Spleen, vulva, Lacrimal gland, Kidney	DLBCL FL ALCL	DLBCL, MALT B-NHL (U), IPSID, PEL, MF
Yang et al,[24] 2011 China	5549	9	2968 (53.5)	WR,GIT NPNS, SKIN	CNS, orbit, Bone, testis thyroid	DLBCL FL SLL	DLBCL,ENK TCL MALT
Yaqo et al,[23] 2011 Iraq	205	7	99 (48.3)	Intestine WR .Nose, Stomach	Same	DLBCL FL	DLBGL BL MALT
Yun et al,[20] 2010 Korea	48	11	48 (100)	_	Adrenal ,ovary Esophagus Pancreas	_	DLBCL (MC)
Nagi et al,[22] 2010 Pak &KSA		5	147	GIT,NPNS Bone. salivary gland	Liver, lung Cervix CNS	DLBCL, MALT FL	DLBCL PTCL BL
Fujita et al,[18] 2009 Japan	847	7	395 (46.5)	GIT, WR Orbit	Bone , skin. CNS, thyroid	DLBCL MALT FL	DLBCL MALT
Lal et al,[17] 2008 Pakistan	557	16	235 (42)	GIT aerodigesti ve	Bone, breast Testis,	All cases DLBCL	
					CNS		
Singh et al,[12] 2003 India	241	3	106 (44)	Tonsil Stomach	Brain, skin Bone, CNS	Diffuse large cell lymphoma (Intermediate grade) (Working formulation	
Present study 2013 North India Kashmir	400	5	96 (24)	GIT WD	CNS, testis Breast, orbit Thyroid	DLBCL FL MCL	DLBCL MALT

NHL; non Hodgkin lymphoma, ENL;, extra nodal non Hodgkin lymphoma, n; number of patients studied, WR; Waldeyer's ring, GIT; gastrointestinal tract including stomach, small and large intestine, NPNS; nose, nasopharynx, and paranasal sinus, CNS; central nervous system including brain and spinal cord, MC; most common,r, DLBCL; diffuse large B cell lymphoma, FL; follicular lymphoma, SLL; small lymphocytic lymphoma, ENKTCL; extranodal natural killer/T cell lymphoma of nasal type, MALT; extra nodal marginal zone lymphoma of mucosa associated lymphoid tissue type, PTCL; peripheral T cell lymphoma, BL; Burkitt lymphoma, ATLL; adult T cell lymphoma/leukemia, B-NHL; B cell non Hodgkin lymphoma morphologically intermediate between Burkitt lymphoma and DLBCL, MF, mycosis fungoides, EBV, Epstein Barr virus, HTLV; Human T-lymphotropic virus1, Pak & KSA; Pakistan and Kingdom of Saudi Arabia.

associated gastritis detected in gastric biopsies on routine Giemsa staining. Seropositivity for HIV was present in 1.08% (1/96) of patients whereas association with HBV were seen in 2.08% of patients . Nine percent (9/96) of the patients were diabetic (type 2) (Figure 2).

Gastrointestinal tract constituted the most common site of pENL (60/96, 62.5%)(41stomach, 5 duodenum/jejunum, and 11 colon appendix 3), followed by waldayer's ring (28/96, 29.16%), nasopharynx and testis each (2/96, 2.08%), , CNS ,orbit, breast, thyroid (1 patient each) were the rare anatomic sites of pENLs observed in our study. (Figure 3).

On IHC, 93/96 (96.87%) of pENL had B immunophenotype whereas T cell phenotype was observed in only 3 patients (3.12%). Diffuse large B-cell lymphoma, not otherwise specified (DLBCL) was the most common histological type observed in 67.7% (65/96), followed by extranodal marginal zone lymphoma of MALT type (19/96, 19.79%). B-NHL unclassifiable (U) (morphologically in between DLBCL and Burkitt lymphoma) , 9.37% (9/96) ,peripheral T cell lymphoma, not otherwise specified (PTL-NOS) were seen in 2.08% (2/96) whereas T-cell rich B-cell lymphoma, in 1.04% (1/96) of patients respectively.

Fig 4.

Fifty three of 96 (54.5%) patients were in stage I/II, 34/96 (35.41%) in stage III, whereas 9/96 (9.37%) were in stage IV. On follow-up (70/96, duration 3 months to 5 years), 40 had complete remission, 16 had progressive disease (4 lost to subsequent follow-up), 4 with relapse with high grade morphology with increased proliferation index, and 6 died due to complication of chemo radiotherapy.

FIG 1 AGE AND SEX DISTRIBUTION OF CASES

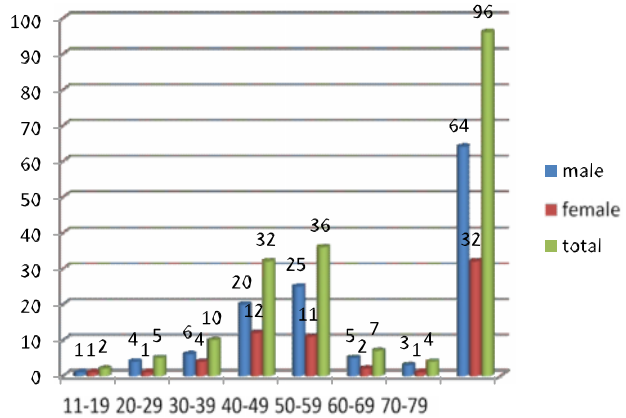


FIG 2 OTHER DISEASES PRESENT AT TIME OF DIAGNOSIS

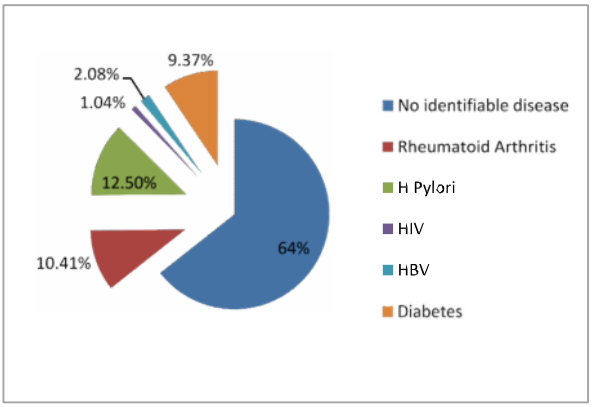


FIG 3 SITES OF INVOLVEMENT BY ENHLS

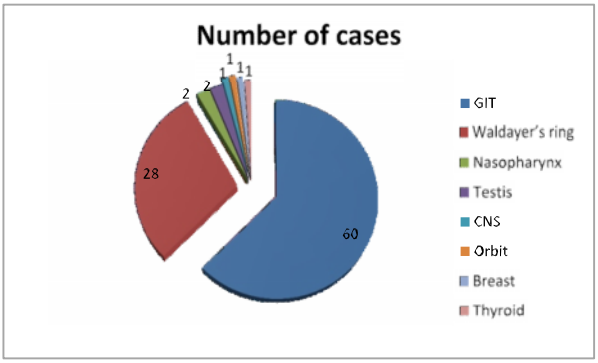


FIG 4 HISTOLOGICAL TYPES OF ENHLS

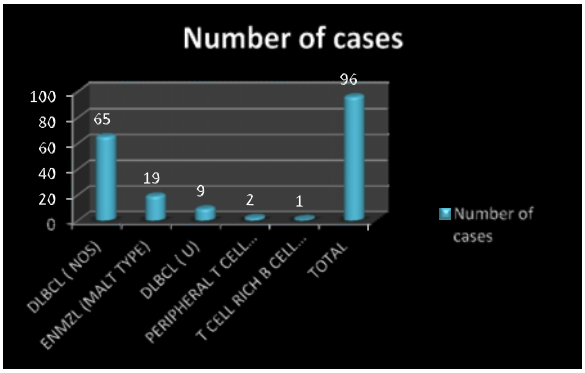


FIG 5 STAGES OF ENHLS

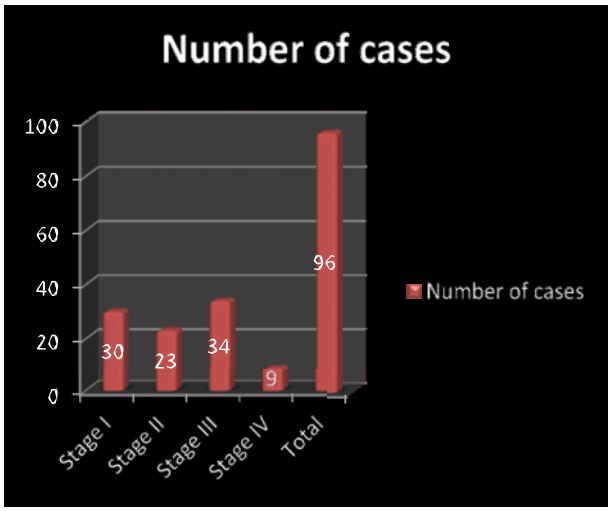
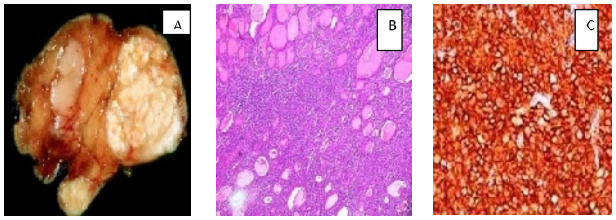
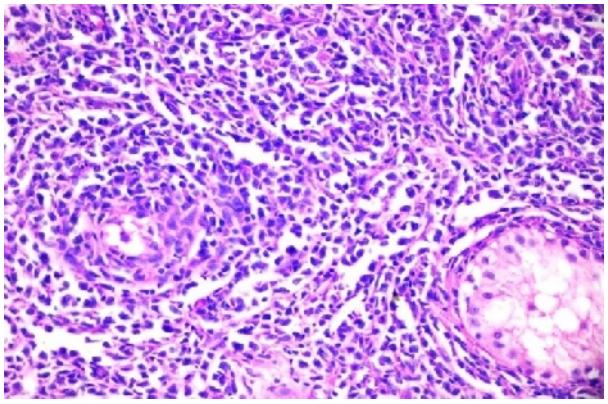


FIG 6



Gross and micrspic picture of thyroid lymphoma varible sized thyroid follicles filled with colloid and sheets of large cells in interfollicular area.diffuse CD20 positivity

FIG 7



Microscopic picture of testicular lymphoma showing seminiferous tubules and interistitium infiltrated by large cells .

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