

# Clinical Features of Non – Hodgkin Lymphoma in Northern India An Analysis of 241 Cases

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## ABSTRACT

**Background:** Geographic variations in incidence, clinical presentation and histological subtypes are known to occur in several cancers. This study was aimed to see if similar differences exist in Non-Hodgkin Lymphoma (NHL) among North Indian population.

**Methods:** Cases of NHL seen at Institute Rotary Cancer Hospital (IRCH), All India Institute of Medical Sciences (AIIMS), New Delhi from January 1997 to December 2000, were analyzed for baseline clinical features and histology.

**Results:** Total cases: 241, median age: 47 years (range 2-84 years), male-female ratio: 2.2:1, primary extranodal NHL: 44.2%, commonest histological subtype: diffuse large cell (6.2% of the cases).

**Conclusion:** Our patients presented at younger median age, had more male to female ratio, had diffuse large cell histology as the most common histological subtype.

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**Key words:** Non-Hodgkin lymphoma, geographic pathology, regional variations in cancer

**Abbreviations:** NHL – Non-Hodgkin Lymphoma

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## Introduction

Incidence of non-Hodgkin lymphoma is rising worldwide. Geographic variations in its incidence and clinical behavior are well known [1]. NHL despite being the commonest lympho-hematopoietic malignancy in India, has lower age-standardized incidence rate (0.8–5.1 males, 0.6–3.1 females) compared to that seen in the USA (16.1 males, 10.8 females). Low grade NHL (follicular lymphoma, chronic lymphocytic leukemia) is more common in the USA, whereas diffuse large B cell lymphoma is more common in India. Burkitt's lymphoma occurs more frequently in tropical Africa, immunoproliferative small intestinal disease (IPSID) in

the Middle East and adult T-cell leukemia / lymphoma (ATLL) in South West Japan and the Caribbean basin [1, 2, 3, 4]. Published Indian data on the demography of NHL is scarce. So we decided to analyze the clinical features of NHL seen at our center.

## Methods

Patients of NHL registered at Institute Rotary Cancer Hospital (IRCH) of All India Institute of Medical Sciences (AIIMS), New Delhi between January 1<sup>st</sup> 1997 and December 31<sup>st</sup> 2000 were included in this study. Medical records of NHL patients were retrospectively reviewed for the epidemiological, clinical and laboratory data. Confirmation of histopathological diagnosis at AIIMS was mandatory for inclusion in the study. Other inclusion criteria were treatment naive and those who received treatment at AIIMS. Patients with FNAC (Fine Needle Aspiration Cytology) based diagnosis were excluded. Working formulation classification of NHL was used for histological classification [4] and Ann Arbor classification was for staging the tumor [5]. Stage at initial presentation was determined on the basis of clinical, radiological and laboratory data available in the medical records.

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## Results

Of the 241 patients included in the study 168 were male and 73 were female with a male to female ratio of 2.2:1. The median age at presentation was 47 years (range 2-84 years). Median symptoms duration was 4 months (range 0.5 – 6 months). 'B' symptoms were present in 104 patients (43.2%). Among the patients 167 (69.3%) had peripheral lymphadenopathy, whereas 107 (44.4%) had axial lymphadenopathy. Cervical nodes were commonly involved (n=138) followed by retroperitoneal (n=77), inguinal (n=34), axillary (n=34), mediastinal (n=22) and mesenteric nodes (n=22). Iliac (n=16), Coeliac (n=11) and porta hepatic nodes (n=9) were rarely involved. pitrochlear (n=6), It was generalized (involvement of 3 or more noncontiguous lymph node areas) in 54 cases (22.4%). Bulky lymphadenopathy was

**Table-1: Distribution of primary extra nodal NHL**

Anatomical Region	n (%)	Distribution Pattern
Head and Neck region	53 cases (22%)	Tonsil-23, Sino nasal tract-6, Nasopharynx-12, Oropharynx-1, Orbit-9, Parotid-1, Thyroid-2
Gastro intestinal region	29 (12%)	Somach-17, Small intestine-4, Colon-5, Ileocaecal region-2, Rectum-1
Other sites		Brain-4, Spine-4, Bone-5, Skin-6, Testis-3, Urinary bladder-2

**Table 2: Histological subtypes, Working Formulation based**

Histological Subtype	n (%)
Small lymphocytic lymphoma	6 (2.5%)
Follicular small cleaved cell	15 (6.2%)
Follicular mixed small cleaved & large cell	5 (2.1%)
Follicular large cell	1 (0.4%)
Diffuse small cleaved cell	11 (4.6%)
Diffuse mixed small cleaved & large cell	11 (4.6%)
Diffuse large cell	146 (60.58%)
Large cell immunoblastic	3 (1.2%)
Lymphoblastic	9 (3.7%)
Small non-cleaved cell	3 (1.2%)
Others*	31 (12.86%)

Others\* include MALT (mucosa associated lymphoid tissue) lymphoma (2 cases), AILD (angio immunoblastic lymphadenopathy with dysproteinemia) lymphoma (1 case), Primary cutaneous T cell lymphoma (1 case), Mycosis Fungoides (2 cases) and Unspecified (25 cases).

seen in 41 patients (17%), malignant pleural effusion in 19 (3%), malignant ascites in 22 (4%) and superior vena cava syndrome in 4 (1.7%) at presentation.

Primary extranodal NHL (when extra nodal site is the only site of disease or the bulk of disease is confined to extranodal sites) [6,7] was seen in 106 cases (44.2%). Head and neck region was the commonest region (53 cases-22%) of extranodal involvement followed by gastrointestinal tract (29 cases-12%). Extranodal disease distribution is shown in Table 1. Diffuse large cell was the commonest histological subtype of NHL seen at our center accounting for 146 cases (60.58%) (Table 2). Unspecified and other histologies accounted for 31 cases.

More than 50% of the patients had advanced stage of III & IV at presentation, stage III - 45 cases (18.4%) and stage IV – 84 cases (35.1%). Early stage was seen in 112 cases, stage I – 55 cases (22.8%) and stage II – 57 cases (23.7%). Bone marrow infiltration was the most frequent reason for stage IV disease (53 patients, 22% of the total cases). Other disease sites leading to stage IV disease were: liver - 9 cases, malignant ascites – 4, malignant pleural effusion – 3, multiple extranodal sites – 6, multifocal bone involvement – 1, brain - 4 and spine – 4 cases. Fluid cytology was positive in 41 cases (ascites 22, pleural fluid 19).

## Discussion

Epidemiological features, clinical presentation and histological subtypes of various types of NHL analyzed in this study revealed many differences from the Western data. These include: younger median age, higher male-female ratio, head and neck as the commonest extranodal site of disease, diffuse large cell as the commonest histology, and higher frequency of stage IV disease. The median age of 47 years noted in our study is 10 years lesser than the median age reported in the Western literature [8,9,10]. 2 earlier studies from AIIMS had reported the median age of 45 and 50 years respectively [1, 11]. Although the exact reason for this earlier occurrence of NHL in India remains unexplained several hypothesis have been proposed [12]. It is speculated that increased frequency of infectious diseases and chronic antigenic stimulation could be the cause. Indians are more exposed to infectious diseases at an early age and this has been proposed as a reason for early peak (1<sup>st</sup> and 2<sup>nd</sup> decade) of Hodgkin disease in India [13]. Different age structure in India (40% population < 15 years compared to 21% in the west) may also be responsible for early median age [12]. Other possible explanations are different genetic make up of Indians and socio-economic factors such as elderly people opting for no treatment [12]. Though males seem to be affected more than females

throughout the world, the ratio of 2.2:1 in this study is higher compared to 1.5:1 reported in this west [14,15,16]. Garg et al had also reported higher male – female ratio (4.5:1) from our center [11]. Social structure favoring males could be a factor for more male prevalence of NHL in males in India, though the exact reasons are not clear.

Extranodal NHL accounts for 44.20% of NHL cases in our series, which is comparable to the reported literature (24-48%) [16,17]. However the frequency of head and neck region NHL is higher in our study (50% of extra nodal NHL, 22% of all NHL). In the Western countries and Singapore, gastrointestinal tract (GIT) is the commonest site of extra nodal disease [18]. Our results are similar to Japanese and Chinese series wherein head and neck region is the commonest extranodal site [13]. The reasons for these regional variations is not clear.

Histological sub-classification of NHL has gone substantial changes with the availability of new immunohistochemical markers. 'Working Formulation' classification used in this study has now been replaced by the REAL and WHO classifications. Similarly availability of monoclonal antibody (anti CD 20 antibody) has also changed the treatment outcome of B cell lymphoma [1]. However we did not use immunohistological markers in our study and our classification is based on light-microscopic appearance of the tumor. As these advanced facilities are not available universally, we consider that our study based mainly on histo-morphology is still relevant.

There is a lower frequency of follicular small cleaved cell NHL (6.2%) in the present study compared to the West (22.5%) and higher frequency (60.58%) of diffuse large cell NHL than reported in the West (19.7%) (18-20). This is consistent with other studies from India and Asia, that also report lower frequency (3.4 – 13.2%) of follicular NHL [20]. At our center Garg et al had earlier reported 13.4 % frequency of follicular NHL [11]. At Tata Memorial Hospital, Bombay, almost similar figure of 11.4% has been reported [21]. Follicular NHL formed only 6.3% of all NHL at Chang Gung Memorial Hospital, Taiwan [13], 2.8% in Thailand [22], 1.1% in Egypt [23] and 2.1% in Lebanon [24]. Incidence of follicular lymphomas continues to be low in Asians even after they migrate to the USA, subsequent generations however record higher incidence suggesting an environmental influence [25]. Histological progression from follicular to diffuse pattern has also been reported [26]; thus, patients presenting late after the onset of symptoms may have an advanced disease and diffuse histological pattern. Although these factors may explain, to a limited extent, the high diffuse to follicular ratio in India, there are other, yet unrecognized,

factors responsible for this geographic variation in the histological pattern of NHL. Studies of Hodgkin disease in India also reveal a high frequency of mixed cellularity and lymphocytic depletion types of lymphoma, known to be associated with poor prognosis, as compared with Western series that report a high incidence of nodular sclerosis type of Hodgkin disease [27]. Whether genetic factors make our population more susceptible to diffuse lymphomas, which are associated with poor prognosis or whether viruses, carcinogens, nutritional or socioeconomic factors are responsible, requires further study.

Advanced stage (III/IV) is more frequent in our population than in the west [46]. It may be either be due to racial difference or due to late diagnosis consequent to poor socioeconomic status and restricted access to tertiary level health care.

## Conclusion

There are differences in the epidemiology, clinical presentation and histological subtypes of NHL in our population as compared to the Western countries. Young median age, more male to female ratio, more of head and neck NHL, high frequency of diffuse large cell histology and advanced stage disease are characteristics of Indian patients.

**Conflicts of Interest :** Nil

**Ethics :** Being a retrospective analysis of medical records, Institute Review Board approval was not required.

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