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Original Article

Non-Hodgkin's Lymphoma in Northern India: An Analysis of Clinical Features of 241 Cases

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Abstract

Background: Geographic variations with regard to incidence, clinical presentation, and histological subtypes are known to occur in several cancers. This study was aimed to see if similar differences existed in non-Hodgkin's lymphoma (NHL) also during pre-immunohistochemical era. **Materials and Methods:** Cases of NHL seen at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, 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%, the most common 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.

Keywords: *Extranodal non-Hodgkin's lymphoma, non-Hodgkin's lymphoma, Northern India*

Introduction

The incidence of non-Hodgkin's lymphoma (NHL) is rising worldwide. In addition, geographic variations in its incidence and clinical behavior are well known.[1] NHL despite being the most common lympho-hematopoietic malignancy in India, has lower age-standardized incidence rate (ASR) (0.8–5.1 males, 0.6–3.1 females) than that seen in the USA (16.1 males and 10.8 females). Low-grade NHL (follicular lymphoma, and 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 in the Middle East and adult T-cell leukemia/lymphoma in South West Japan and the Caribbean basin.[1-4] Despite being a large country publications for NHL from India in general and northern India, in particular, are limited. The subclassification of NHL has gone substantial changes with the availability of new immunohistochemical markers, and also the availability of monoclonal antibody (anti-CD 20 antibody) has changed the treatment outcome of B-cell lymphoma,[1] but this study predates these or when these parameters or treatment options were not freely available to our patients and diagnosis was based mainly on morphology. Hence, we decided to analyze the clinical features of NHL seen at our center.

Materials and Methods

Patients of NHL registered at Institute Rotary Cancer Hospital (IRCH), All India Institute of Medical Sciences (AIIMS) between January 1, 1997 and December 31, 2000 were included in this study. The IRCH files of the patients were taken from the record section and scrutinized for the epidemiological, clinical, and laboratory data. Confirmation of the 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 fine-needle aspiration cytology based diagnosis were excluded.

Working formulation classification of NHL was used for classification.[4] Ann Arbor classification was used to staging the patients.[5] The stage at initial presentation was determined on the basis of clinical, radiological, and laboratory data available in the files.

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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. "B" symptoms were present in 104 patients (43.2%).

One hundred and sixty-seven patients (69.3%) had peripheral lymphadenopathy, whereas 107 (44.4%) had axial lymphadenopathy [Table 1]. It was generalized (involvement of 3 or more noncontiguous lymph node areas) in 54 cases (22.4%). Individual sites of lymphadenopathy are shown in Table 1. Bulky lymphadenopathy was seen in 41 patients (17%) and superior vena cava syndrome in 4 (1.7%) at presentation.

Primary extranodal NHL (when the extra nodal site is the only site of disease, or the bulk of disease is confined to extranodal sites)[6] was seen in 106 cases (44.2%). Head and neck region was the most common region (53 cases - 22%) of extranodal involvement followed by gastrointestinal tract (GIT) (29 cases - 12%). Various sites and sub sites of extranodal disease are shown in Table 2.

Table 1: Clinical presentation of 241 cases

Clinical Characteristic	Clinical details
Age	Median 47 years (range 2-84)
Sex	Male 168, female 73, male female ratio - 2.2:1
Symptom duration	Median 4 months (range 0.5-6.0)
"B" symptoms	104 patients (43.2%)
Peripheral lymphadenopathy	167 patients (69.3%), generalized - 54, cervical - 138, axillary - 34, epitrochlear - 6, inguinal - 34
Axial lymphadenopathy	107 patients (44.4%), mediastinal - 22, hilar - 14, retroperitoneal - 77, coeliac - 11, portahepatic - 9, mesenteric - 22, iliac - 16
Bulky lymphadenopathy	41 patients (17%)
SVC features*	4 patients (1.7%)
Malignant cell positive pleural effusion	19 patients (3%)
Malignant cell positive ascites	22 patients (4%)

*SVC features – Superior vena cava obstruction features

Table 2: Primary extra nodal NHL, 106 cases (44.2%)

Extra nodal site	Number of cases
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 cases (12%), stomach - 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

The diffuse large cell was the most common histological subtype based on Working Formulation classification [Table 3]. It accounted for 146 cases (60.58%). Other subtypes included follicular small cleaved cell – 15 (6.2%) cases, diffuse small cleaved cell – 11 (4.6%), diffuse mixed cell – 11 (4.6%), lymphoblastic – 9 (3.7%), follicular mixed cell – 5 (2.1%), large cell immunoblastic – 3 (1.2%), small noncleaved cell – 3 (1.2%), and follicular large cell – 1 (0.4%). Unspecified and other histologies accounted for 31 cases.

More than 50% of the patients had advanced Stage of III and IV at presentation, Stage III – 45 cases (18.4%), and Stage IV – 84 cases (35.1%) [Table 4]. 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) [Table 5]. 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

NHL, despite being the most common lympho-hemopoietic malignancy in India, has lower ASR (0.8–5.1 males, 0.6–3.1 females) than that seen in the USA (16.1 males,

Table 3: Histological subtypes, working formulation based

Histological subtype	Number of patients (%)
Small lymphocytic lymphoma	6 (2.48)
Follicular small cleaved cell	15 (6.22)
Follicular mixed small cleaved and large cell	5 (2.07)
Follicular large cell	1 (0.41)
Diffuse small cleaved cell	11 (4.56)
Diffuse mixed small cleaved and large cell	11 (4.56)
Diffuse large cell	146 (60.58)
Large cell immunoblastic	3 (1.24)
Lymphoblastic	9 (3.73)
Small noncleaved cell	3 (1.24)
Others*	31 (12.86)

*Others include MALT lymphoma (2 cases), AILD lymphoma (1 case), Primary cutaneous T-cell lymphoma (1 case), Mycosis fungoides (2 cases) and unspecified (25 cases). MALT – Mucosa associated lymphoid tissue; AILD – Angio immunoblastic lymphadenopathy with dysproteinemia

Table 4: Ann Arbor stage distribution of 241 cases

Stage	Number of patients (%)
I	55 (22.82)
II	57 (23.65)
III	45 (18.67)
IV	84 (34.85)

Table 5: Distribution of Ann arbor Stage IV patients based on site of involvement, 84 cases

Site of involvement	Number of patients (%)
Bone marrow	53 (63.09)
Liver	9 (10.71)
Malignant cell positive ascites	4 (4.76)
Malignant cell positive pleural effusion	3 (3.57)
Multiple extra nodal sites	6 (7.14)
Multi focal bone involvement	1 (1.19)
Brain	4 (4.76)
Spine	4 (4.76)

10.8 females).[7] 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 most common extranodal site of disease, diffuse large cell as the most common histology, and higher frequency of Stage IV disease.

The median age of 47 years in the study is a decade earlier than reported in the Western literature.[7-9] Two earlier studies from AIIMS had reported the median age of 45 and 50 years, respectively.[1,10] The reason for this earlier occurrence of NHL in India remains unexplained. However, many reasons have been suggested for this.[11] It is speculated that increased frequency of infectious diseases and chronic antigenic stimulation may be responsible. Indians are more exposed to infectious diseases at an early age, and this has been proposed as a reason for early peak (1st and 2nd decade) of Hodgkin's disease in India;[12] whether this applies to NHL also, remains unanswered. Different age structure in India (40% population <15 years compared to 21% in the west) may also be responsible for early median age.[11] Other possible reasons could be as follows: Different genetic makeup of Indians and socioeconomic factors with older people not reporting for treatment.[11]

Although 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.[13,14] Garg *et al*. had also reported higher male – female ratio (4.5:1) at our center.[10] Social structure-favoring males might be a factor for more male prevalence of NHL in males in India, though the exact reasons are not clear.

Extranodal non-Hodgkin's lymphoma

Extranodal NHL accounts for 44.20% of NHL cases in our series, which is comparable to the reported literature (24%–48%). 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 west, GIT is the most common site of extra nodal disease.[15] Our results are similar to Japanese and Chinese series; in these countries also, head and neck region is the most common extranodal site.[12] However in Singapore, GIT is the most common site as is the case in the West. The reasons for these variations need to be discovered.

Histology

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%).[15] This is consistent with other studies from India and Asia, which also report lower frequency (3.4%–13.2%) of follicular NHL.[12] At our center Garg *et al*. had earlier reported 13.4% frequency of follicular NHL.[10] At TMH Bombay, the almost similar figure of 11.4% has been reported.[16] Follicular NHL formed only 6.3% of all NHL at Chang Gung Memorial Hospital, Taiwan,[12] 2.8% in Thailand,[17] 1.1% in Egypt[18] and 2.1% in Lebanon.[19] The incidence of follicular lymphomas continues to be lower in Asians even after they immigrate to the USA, subsequent generations, however, record higher incidence suggesting an environmental influence.[20] Histological progression from follicular to the diffuse pattern has been reported;[21] 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 the follicular ratio in India, there are other, yet unrecognized, factors responsible for this geographic variation in the histological pattern of NHL. Studies of Hodgkin's 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's disease.[22] 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.

Stage distribution

Advanced stage (III/IV) is more frequent in our population than in the west (46). It may be either be due to late diagnosis due to poor socioeconomic status denying access to tertiary care or biological differences.

Conclusion

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

Limitations

It has a limitation in the form of being a retrospective study. Moreover, "Working Formulation" classification used in this study has now been replaced by the REAL and WHO classifications. In addition, there is a time delay in publication of this manuscript.

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Conflicts of interest

There are no conflicts of interest.

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