

## PRESENTATION, STAGING AND DIAGNOSIS OF LYMPHOMA: A CLINICAL PERSPECTIVE

Mozaffer Rahim Hingorjo, Sadiqa Syed

Department of Physiology, Fatima Jinnah Dental College, Karachi, Pakistan.

**Background:** Due to lack of awareness among health professionals, lymphoma is often misdiagnosed. This study was done to evaluate the clinical features and histopathologic subtypes of lymphoma. **Methods:** Sixty diagnosed cases of lymphoma were selected (aged 12–65 years) from medical units of Civil Hospital Karachi, during 1993 to 1998. Clinical history, physical examination and basic laboratory investigations including imaging procedures were done in all the patients. The diagnosis of lymphoma was based on histology, following the International Working Formulation classification system. This included lymph node biopsy and in some cases, biopsy of the bone marrow. The Ann Arbor Staging Classification was used to classify the extent of disease. **Results:** Out of 60 cases of lymphoma, 81.6% (49 cases) were diagnosed as non-Hodgkin's lymphoma and 18.3% (11 cases) as Hodgkin's disease, with an overall male predominance. Both categories exhibited a bimodal age distribution. Lymphadenopathy was the commonest presenting features in both the types of lymphomas; however, patients with Hodgkin's disease had a prominence of 'B' symptoms, whereas abdominal signs and symptoms were more common in non-Hodgkin's lymphoma. On histopathology, majority of non-Hodgkin's lymphomas (91.8%) showed a diffuse pattern, while mixed cellularity was the commonest type seen in Hodgkin's disease (81.8%). **Conclusion:** Non-Hodgkin's lymphoma was 4 times more common than Hodgkin's disease. The vast clinical spectrum of lymphoma sometimes delays its diagnosis, leading to its eventual presentation in late stages. A general awareness is hence required among the health professionals regarding its varied clinical presentations.

**Keywords:** Non-Hodgkin's lymphoma, Hodgkin's disease, Lymphadenopathy, Hepatomegaly, Splenomegaly

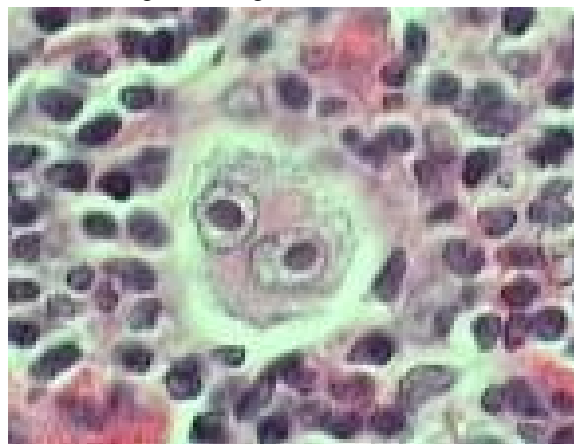
### INTRODUCTION

Lymphomas are malignant disorders of cells residing in lymphoid tissues and are classified into two main types; Hodgkin's Disease (HD), and non-Hodgkin's lymphoma (NHL), depending upon histopathologic evidence on biopsy taken from an enlarged lymph node.

Lymphoma can occur at any age; however, it has a bimodal presentation with one peak in early years of life and other after middle age. Patients with lymphoma usually present with constitutional symptoms of weight loss, fever and night sweats or because of enlarged lymph nodes. Symptoms may also develop due to pressure effects of lymph nodes on surrounding structures or due to involvement of extra nodal sites such as gastrointestinal tract (GIT), central nervous system (CNS), liver, or bone, thus leading to atypical presentations.<sup>1</sup>

Due to the varied clinical picture, many patients are misdiagnosed and treated for diseases like tuberculosis,<sup>2</sup> systemic lupus erythematosus, etc for a long time before coming to the correct diagnosis. Sometimes, benign disorders including ordinary infections and other non-neoplastic conditions may be interpreted as malignant lymphoma and unnecessarily subjected to surgery and / or chemotherapy.<sup>3</sup> The diagnosis of lymphoma involves histopathological findings on biopsy of an enlarged lymph node from a relevant side, aided further by invasive or non-invasive procedures to confirm the extent of disease, and to

formulate a proper therapeutic plan. Primary to the diagnosis of Hodgkin's disease is the presence of malignant Reed-Sternberg cell in an appropriate cellular background (Figure-1).



**Figure-1: Reed Sternberg cell**

(Courtesy of Dr. Donald Innes, Department of Pathology, University of Virginia Health Sciences Centre, Charlottesville, VA 22908)

These are giant malignant cells characteristic of Hodgkin's disease, having large, abundant cytoplasm, double or multiple nuclei, with prominent nucleoli surrounded by distinctive clear zone; together they give an 'owl's eye' appearance to the cell.

The classification of both HD and NHL is continuing to evolve incorporating not only

histopathologic data, but also immunophenotypic, genotypic and clinical characteristics<sup>4</sup> to design a treatment using varying combinations of chemotherapy, radiotherapy and immunotherapy. The most common classification system for NHL during 1980's–1990's was the International Working Formulation (IWF), that was based purely on the morphological characteristics of the lymphoma, though later some immunophenotyping was added.<sup>5</sup> Still newer systems evolved due to development of advanced techniques to further define NHL. These included the Revised European American Lymphoma (REAL)<sup>6</sup> and its successor WHO classification<sup>7</sup> that takes into account in addition to morphology, the cell phenotype, genotype, clinical features, and demographic data. It is, however, difficult in developing countries to fully adapt to these recent classifications due to the limited resources available and lack of appropriate epidemiological data, therefore the IWF has been followed here.<sup>8</sup>

Lymphomas are treatable and frequently curable malignancies; however, a proper staging evaluation is required to categorize them into different stages so as to follow an appropriate therapeutic plan. The Ann Arbor staging system<sup>9</sup> assigns an anatomic stage to the lymphoma by focusing on the number of tumour sites (nodal and extra nodal), location, and the presence or absence of systemic symptoms.

This study was planned to evaluate the different clinical presentations of lymphoma and the patterns of disease distribution.

## PATIENTS AND METHODS

In this cross sectional study, sixty diagnosed cases of lymphoma were selected from medical units of Civil Hospital Karachi, during the period 1993 to 1999. The study included patients from age group 12 to 65 years. Excluded from the study were patients having chronic lymphocytic leukaemia, plasma cell myeloma, precursor B and T lymphoblastic leukaemia and lymphomatoid granulomatosis grades 1 and 2.

Detailed history was taken and clinical examination done. Initial laboratory evaluation included a blood cell count, erythrocyte sedimentation rate (ESR), serum electrolytes and urinalysis. The diagnosis of lymphoma was based on histology, following the International Working Formulation classification system. In this regard, lymph node biopsy was performed by surgical resection in most cases, and bone marrow biopsy in selected few.<sup>10</sup> The Ann Arbor Staging Classification<sup>9</sup> was used to classify the extent of disease, for which further investigations were carried out. These included liver function test, renal

function test, serum calcium and uric acid levels. Cytological analysis of fluid (cerebrospinal, peritoneal, pleural, and pericardial) was done where necessary. Imaging procedures included chest X-ray or chest computed tomography (CT), ultrasonograms or CT of the abdomen and in three cases CT of brain.

## RESULTS

Out of 60 cases under study, 81.6% (49 cases) belonged to NHL with a male to female ratio of 6:1, while 18.3% (11 cases) were diagnosed as having HD with a male to female ratio of 4.5:1. Our study exhibited a bimodal distribution in age. For NHL the first peak occurring in age range of 12–13 years and second peak between 52–62 years. For HD initial peak was observed in 12–21 years group while later peak starting around the age of 60 years. The incidence of lymphoma in males was higher in earlier years, but as age advanced, the incidence in female increased and approached nearly that of males. Lymphadenopathy was a very common finding on general examination in both NHL and HD. The commonest site in NHL was para-aortic, followed by cervical and axillary, whereas the commonest site in HD was cervical, followed by axillary and inguinal. Many patients had other signs and symptoms as well; the details of which are shown in Table-1. Eighteen cases of NHL (36.7%) presented with one or more of the 'B' symptoms as compared to 10 cases of HD (90.9%). These include fever (temperature >38 °C), drenching night sweats, and unexplained loss of >10% body weight within the preceding 6 months.

Staging was done according to the Ann Arbor Staging Classification and it was observed that one patient of HD was in stage I & II each, two in stage III, while seven patients had stage IV disease. For NHL, only two patients were in stage I and four in stage II disease. The majority had stage III (14 patients) and stage IV (29 patients) disease.

Most cases of NHL (34.6%) were classified as diffuse small cleaved cell lymphoma and the remainders were as follows: 24.4% as diffuse large cell lymphoma; and 16.3% as diffuse mixed small and large cell lymphoma. Less common varieties were small lymphocytic lymphoma, follicular small cleaved cell lymphoma, large cell immunoblastic lymphoma, and lymphoblastic lymphoma. By far the largest individual classification categories were diffuse pattern (45 cases, 91.8%) and follicular pattern (4 cases, 8.1%). Majority of the cases of HD belonged to mixed cellularity group (81.8%) and only 2 cases had Nodular sclerosis (18.1%) (Table-2).

**Table-1: Clinical manifestations of Lymphoma**

Symptoms	NHL	HD	Signs	NHL	HD
Fever	67.3 %	90.9 %	Anemia	100 %	100 %
Weight loss	24.8 %	81.8 %	Jaundice	30.6 %	27.2 %
Swellings in neck, axilla or groin	61.2 %	90.9 %	Hepatomegaly	83.6 %	72.7 %
Abdominal pain	55.1 %	27.2 %	Splenomegaly	44.8 %	81.8 %
Vomiting	30.6 %	45.4 %	Ascites	28.5 %	36.3 %
Headache	18.3 %	18.1 %	Abdominal tenderness	30.6 %	18.1 %
Joint pains	4.0 %	45.4 %	Abdominal Mass	28.5 %	0 %
B Symptoms	36.7 %	90.9 %	Peripheral edema	4.0 %	18.1 %
<b>Lymphadenopathy</b>					
Detected clinically				59.1 %	90.9 %
Detected after further investigation				81.6 %	100 %

**Table-2: Histopathology of Non-Hodgkin's Lymphoma & Hodgkin's Disease**

Non-Hodgkin's Lymphoma		
Classification (by International Working Formulation)	Cases	%
Diffuse small cleaved cell lymphoma ( <i>diffuse</i> )	17	34.6
Diffuse large cell lymphoma ( <i>diffuse</i> )	12	24.4
Diffuse mixed small & large cell lymphoma ( <i>diffuse</i> )	8	16.3
Small lymphocytic lymphoma ( <i>diffuse</i> )	4	8.1
Large cell immunoblastic lymphoma ( <i>diffuse</i> )	2	4.0
Lymphoblastic lymphoma ( <i>diffuse</i> )	2	4.0
Follicular small cleaved cell lymphoma ( <i>follicular</i> )	4	8.1
Grade		
Low	5	10.2
Intermediate	38	77.5
High	6	12.2
Hodgkin's Disease		
Classification	Cases	%
Mixed cellularity	9	81.8
Nodular sclerosis	2	18.1

**DISCUSSION**

Like many other diseases, lymphoma also shows geographical variations in natural history, clinical presentation, and histological subtypes. In the present study, the ratio of NHL to HD was 4:1 (approx) which compares favourably with other studies.<sup>11,12</sup> A bimodal distribution in age was also noted, for both NHL and HD. The initial peak was observed early; for NHL it was 12–13 years and for HD it was 12–21 years.<sup>13</sup> The incidence of lymphoma in males was higher in earlier years, but as age advanced, the incidence in females increased and approached nearly that of males. These findings were consistent with studies conducted previously.<sup>14</sup> The bimodal distribution of lymphoma may be due to the relative immune deficient status in these age groups. This is in turn dependent upon environmental influences, such as common viral infections, and socioeconomic factors.<sup>15</sup> Epstein Barr virus, for example, has a strong causal association with Hodgkin's disease.<sup>16</sup> Improving the standard of living delays the early peak of occurrence of lymphoma up to young adulthood. This may explain the early peak of lymphoma in developing countries, as also was in our study.<sup>17</sup> On the contrary; the incidence of lymphoma in

older age group alters little between populations and is not related to social status.<sup>18</sup>

The clinical presentation of NHL and HD were distinctive, with HD presenting with regional enlargement of single group of peripheral lymph nodes as opposed to disseminated nodal involvement in NHL. Furthermore, most patients with HD presented with the 'B' symptoms, whereas, apart from fever, most patients with NHL had abdominal pain and abdominal mass.<sup>1</sup>

According to World Health Organization (WHO), morphological diagnosis of NHL relies on cytological details, although the development of new technologies has helped to define several clinical entities. HD and some forms of NHL tend to be sclerotic, and require a structural evaluation, possible only with excisional biopsy. Fine needle aspiration cytology (FNAC) though minimally invasive, produces suboptimal material and reveals scanty neoplastic cells. Recent advances attempting at increasing the specificity of FNAC by combining it with immunoflow cytometry (IFC) and immunohistochemistry (IHC), have proven unsuccessful for certain lymphomas and excisional biopsy is still generally recommended.<sup>19</sup>

Lymphadenopathy is a common sign of benign and malignant disorder.<sup>20</sup> Presence of lymphoid cells in FNAC are usually considered to be associated with the diagnosis of lymphoma; however, there are other types of lymphoid infiltrates that may be misleading e.g. granulomatous infiltrates like tuberculosis,<sup>2</sup> lymphoid infiltrates in extra nodal sites, and neoplasm containing lymphocytes.<sup>21</sup> Due to this, many times patients with lymphoma were misdiagnosed and treated incorrectly with anti-tuberculous drug therapy as this is the most prevalent condition in our population. On the contrary, some patients with benign conditions like Kikuchi's disease are subjected to unnecessary surgery or chemotherapy because of their clinical and histological resemblance to lymphoma.<sup>3</sup>

Majority of cases of NHL in this study were of intermediate grade, with less frequent high and low grades and this is the commonest variety seen in western

studies also. Diffuse lymphoma (DL) formed the major proportion whereas follicular lymphoma (FL), although having a better prognosis, was infrequent. This is consistent with studies from Western and Asian countries. One study has explored the possible geographic variation in frequency of FL and hypothesized that different causative or genetic factors are involved in the development of FL in different regions.<sup>22</sup> In the present study, mixed cellularity was the dominant variety of lymphoma seen in Hodgkin's disease, as opposed to nodular sclerosis seen in developed countries.<sup>1</sup> The above pattern of clinicopathologic features seen in malignant lymphomas was consistent with that observed in other Asian studies, distinguishing them from disease encountered in the Western world.<sup>11-13, 23-25</sup>

## CONCLUSION

- Lymphoma presents commonly as lymphadenopathy, fever, weight loss and hepatomegaly with a close resemblance to tuberculosis and other disorders.
- There is a sharp rise in the incidence of extra-nodal primary lymphoma with wide variations in the presentation of the disease due to involvement of sites such as gastrointestinal tract, central nervous system, vagina and cervix etc. This may pose differential diagnosis problems to health practitioners in daily practice, leading to incorrect diagnosis and management, till the disease reaches a very advanced stage.
- A general awareness regarding the clinical manifestations of lymphoma, along with usage of advanced investigative techniques, may lead to early diagnosis of this relatively curable disease.

## REFERENCES

1. Jose BO, Koerner P, Spanos WJ Jr, Paris KJ, Silverman CL, Yashar C, *et al.* Hodgkin's lymphoma in adults – clinical features. *J Ky Med Assoc* 2005;103:15–7.
2. Al-Mobeireek AF, Arafah M, Siddiqui N. An African male with cough, hemoptysis, weight loss and hypercalcemia: TB or not TB? *Eru Respir J* 2002;20:1060–3.
3. Phelan E, Lang E, Gormley P, Lang J. Kikuchi-Fujimoto disease: a report of 3 cases. *Ear Nose Throat J* 2007;86:412–3.
4. Young, Iland. Clinical perspectives in lymphoma. *Internal Medicine Journal* 2007;37:478–84.
5. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112–35.
6. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML *et al.* A revised European–American classification of lymphoid

neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361–92.

7. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2001.
8. Pongpruttipan T, Sithinamsuwan P, Rungkaew P, Ruangchiraurai R, Vongjirad A, Sukpanichnant S. Pitfalls in classifying lymphomas. *J Med Assoc Thai* 2007;90:1129–36.
9. Armitage JO. Staging non-Hodgkin lymphoma. *CA Cancer J Clin* 2005;55:368–76.
10. Franco V, Tripodo C, Rizzo A, Stella M, Florena AM. Bone marrow biopsy in Hodgkin's lymphoma. *Eur J Haematol* 2004;73:149–55.
11. Peh SC, Kim LH, Thanaletchimy N, Chai SP, Poppema S. Spectrum of malignant lymphomas in Klang Hospital, a public hospital in Malaysia. *Malays J Pathol* 2000;22:13–20.
12. Haddadin WJ. Malignant lymphoma in Jordan: a retrospective analysis of 347 cases according to the World Health Organization classification. *Ann Saudi Med* 2005;25:398–403.
13. Shome DK, George SM, Al-Hilli F, Satir AA. Spectrum of malignant lymphomas in Bahrain. Leitmotif of a regional pattern. *Saudi Med J* 2004;25:164–7.
14. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: Non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000;92:1240–51.
15. Landgren O, Caporaso NE. New aspects in descriptive, etiologic, and molecular epidemiology of Hodgkin's lymphoma. *Hematol Oncol Clin North Am* 2007;21:825–40.
16. Dinand V, Dawar R, Arya LS, Unni R, Mohanty B, Singh R. Hodgkin's lymphoma in Indian children: prevalence and significance of Epstein-Barr virus detection in Hodgkin's and Reed-Sternberg cells. *Eur J Cancer* 2007;43:161–8.
17. Flavell KJ, Murray PG. Hodgkin's disease and the Epstein-Barr virus. *Mol Pathol* 2000;53:262–9.
18. Gutensohn NM. Social class and age at diagnosis of Hodgkin's disease; new epidemiologic evidence on the "two-disease" hypothesis. *Cancer Treat Rep* 1982;66:689–95.
19. Mayall F, Darlington A, Harrison B. Fine needle aspiration cytology in the diagnosis of uncommon types of lymphoma. *J Clin Pathol* 2003;56:821–5.
20. Olu-Eddo AN, Ohanaka CE. Peripheral lymphadenopathy in Nigerian adults. *J Pak Med Assoc* 2006;56:405–8.
21. Song JY, Cheong HJ, Kee SY, Lee J, Sohn JW, Kim MJ, *et al.* Disease spectrum of cervical lymphadenitis: analysis based on ultrasound-guided core-needle gun biopsy. *J Infect* 2007;55:310–6.
22. Biagi JJ, Seymour JF. Insights into the molecular pathogenesis of follicular lymphoma arising from analysis of geographic variation. *Blood* 2002;99:4265–75.
23. Sahni CS, Desai SB. Distribution and clinicopathologic characteristics of non-Hodgkin's lymphoma in India: a study of 935 cases using WHO classification of lymphoid neoplasms (2000). *Leuk Lymphoma* 2007;48:122–33.
24. Aziz Z, Rehman A, Akram M, Saeed A. Non-Hodgkin's lymphoma in Pakistan: a clinicopathological profile of 175 patients. *J Pak Med Assoc* 1999;49:11–5.
25. Siddiqui N, Ayub B, Badar F, Zaidi A. Hodgkin's lymphoma in Pakistan: a clinico-epidemiological study of 658 cases at a cancer center in Lahore. *Asian Pac J Cancer Prev* 2006;7:651–5.

## Address for Correspondence:

**Dr. Mozaffer Rahim Hingorjo**, Assistant Professor, Department of Physiology, Fatima Jinnah Dental College, AM-1/B, Block-D, Bhattai Colony, Korangi Creek, Karachi-31 (14900), Pakistan. Tell: +92-21-6641218, Cell: +92-333-2286618  
**E-mail:** muzaffer\_rahim@hotmail.com