Pakistan J. Zool., vol. 44(5), pp. 1367-1372, 2012.

Incidence and Clinical Manifestation of Lymphoma in Central Punjab

Tamseela Mumtaz,[1] Nabila Roohi[1]* and M. Waheed Akhtar[2]
[1]Department of Zoology, University of the Punjab, Lahore-54590, Pakistan
[2]School of Biological Sciences, University of the Punjab, Lahore-54590, Pakistan

Abstract.- Delayed diagnosis in lymphoma deteriorates the health eminence resulting in pitiable prognosis and poor health management. The aim of the study is to estimate the burden and clinical presentation of lymphoma in Pakistan. A total of 334 newly diagnosed cases of lymphoma were registered in the study. Followed by histopathology, WHO classification and Ann Arbor staging was done to assign subtype and extent of disease. It was found that the incidence of non Hodgkin's lymphoma (71%) was greater than Hodgkin's disease (29%) and both present bimodal distribution in age. Male patients dominate female patients in both cases (2.5:1). Lymphadenopathy of cervical region is primary site in 44% of cases while 20% cases were extranodal. Histopathology show 66% mixed cellularity variant in Hodgkin's and 37% diffuse B cell pattern in Non Hodgkin's lymphoma. Ann Arbor staging reveals that 28% cases present with stage I and 38% show stage IV. To conclude, Non Hodgkin's lymphoma is 2 times more frequent than Hodgkin's lymphoma with greater male contribution. Due to complicated classification, delayed diagnosis resulted in late stage presentation. Health awareness is needed both for physicians and general population.

Key words: Lymphoma, lymphadenopathy, incidence of lymphoma

INTRODUCTION

Lymphatic system, comprising of lymph nodes, lymphatic vessels and lymphoid tissues, is running parallel to the blood circulatory system. The primary lymphoid tissues generate two major types of cells, B lymphocytes and T lymphocytes. Lymphoma is a group of cancers that affect these lymphocytes. It is malignant transformation of either B cell or T cell or their subtypes (Rosen *et al*., 2008). These abnormal lymphocytes may travel from one lymph node to another and some time to remote organs via lymphatic system. Care should be taken to assign the primary site/site of origin as it strappingly affects treatment modality. The primary site may be nodal when malignant cells originate from lymph nodes and is extranodal when develop from the organs other than lymphatic system such as gastrointestinal tract, hypochondrium, paranasal sinuses, central nervous system etc. Nodal lymphoma may invade the nearby organ involving extranodal sites and vice versa (Friedberg *et al*., 2008).

Lymphoma, on broad spectrum, classifies into two major categories, Hodgkin's lymphoma (HL) and non Hodgkin's lymphoma (NHL) depending upon histopathologic evidence on biopsy taken from an enlarged lymph node. Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage and has characteristics Reed Sternberg cells 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 cells. It has five subtypes, the common are, mixed cellularity and nodular sclerosis. Non Hodgkin's lymphoma may develop from B or T cells and has about 30 different subtypes (Wilson and Armitage, 2008). Since there are so many different types of lymphomas, its classification is very complicated (Jaffe and Pittaluga, 2005). Many of these subtypes look similar but they are functionally quite different and respond to different type of therapies with different probability of cure (Gribben and LaCasce, 2005). Diffuse large B cell Lymphoma is most common and is potentially curable while Mantle cell lymphoma is unique subtype B cell lymphoma and is potentially incurable (Wu and Keating, 2006; Abramson and Shipp, 2005; Ghobrial *et al*., 2005).

Due to the varied clinical picture, many patients are misdiagnosed and treated for diseases like tuberculosis (Al-Mobeireek *et al*., 2002), systemic lupus erythematosis, etc for a long time before coming to the correct diagnosis. Sometimes,

* Corresponding author: nabilaruhi@gmail.com
0030-9923/2012/0005-1367 $ 8.00/0

benign disorders including ordinary infections, sebaceous cysts and other non-neoplastic conditions may be interpreted as malignant lymphoma and unnecessarily subjected to surgery and/or chemotherapy (Phelan *et al*., 2007). The first sign of lymphoma is painless enlarged lymph nodes accompanying fever for more than 3 days. Usually patient presents with low grade fever, unexplained weight loss and drenching night sweats. Confirmed diagnosis is established on the basis of histopathology findings followed by fine needle aspiration or biopsy of relevant site. Histopathology clearly marks the morphology of cells, their subtypes and resemblance to the normal cells.

Clinically non Hodgkin's lymphoma is dividing into low grade, intermediate and high grade. A high grade lymphoma has cells that look quite different from the normal cells and multiply rapidly hence aggressive in nature while low grade lymphoma cells look much similar to normal cells, multiply slowly and are indolent. Lymphoma is also categorized on the basis of tumor burden for appropriate treatment. The Ann Arbor Staging System (Armitage, 2005) is the most popular system for classifying lymphoma in different stages on the basis of number of tumor sites involved (nodal and extra nodal), location, and the presence or absence of B symptoms. The purpose of the present study is to assess the prevalence of lymphoma and its extent at the time of presentation to evaluate health awareness in population.

MATERIALS AND METHODS

In this cross sectional study, 334 newly diagnosed patients of both types of lymphoma, from central Punjab were registered in Institute of Nuclear Medicine and Oncology, Lahore during the year 2009. The study includes patients of all ages and both sexes. Excluded from the study were the patients having lymphocytic leukemia and hepatitis. Informed consent was obtained from individual patients for collecting demographic and disease data on pre designed questionnaires. Initial laboratory evaluation included complete blood count, differential leukocytes count, erythrocyte sedimentation rate, serum electrolytes and urine analysis. Further investigation includes biochemical tests like renal function test, liver function test, total protein and serum creatinine etc. Specific tests such as lactate dehydrogenase and β2 were microglobulin also performed. Final diagnosis was established by Fine needle aspiration and excision biopsy of enlarged lymph node. Some cases were diagnosed by bone marrow biopsy. Histopathology confirms the specific subtype and grade of lymphoma. With the help of radiology imaging such as ultrasonogram, magnetic resonance imaging, computer tomographic scan etc., staging and extent of disease assigned by using American Joint Commission on Cancer (AJCC) staging manual and Surveillance Epidemiology End Result (SEER) summary stage, respectively (Frederick and David, 2000; Young *et al*., 2001).

Table I.- Age and stage distribution in HL and NHL.

Diagnosis	Age ≤30		Age 31≥100		366
	Male %	Female %	Male %	Female %	Total 367 368
HL	11	8	8	4	31
NHL	14	2	42	11	69
Ann Arbor Staging					
Stage	**I (%)**	**II (%)**	**III (%)**	**IV (%)**	
HL	28.1	10.4	44.8	16.7	
NHL	22.2	14	19	45.3	

RESULTS

Out of 334 cases under study, 71% (238) cases belonged to NHL with male to female ratio 1.5: 1 while 29% (96) cases were diagnosed having HL with male to female ratio 2:1. Accordingly the picture depicted that males of all ages were more affected with disease than females. Our study showed that young peoples were relatively more vulnerable to HL than NHL which was common in adults having age greater than 50 years (Table I). Graphical representation of frequency of age exhibited bimodal distribution where the first peak appears between 20-29 years, both in HL and NHL whereas, in NHL, the second larger peak stuck between 50-59 years. On the other hand, HL hit the other high point at 40-49 years (Fig. 1). On general examination, lymphadenopathy was the commonest finding and 100% patients presented with enlarged

lymph node of any site. The most frequent primary sites were axillary and abdominal lymph node (14% each) followed by lymph node of head neck and face (44%). It was also observed that incidence of malignant extranodal site was also very high (20%) so was evident the abnormal lymphocyte growth outside the lymphatic system (Fig. 2). All extranodal lymphomas were non Hodgkin's.

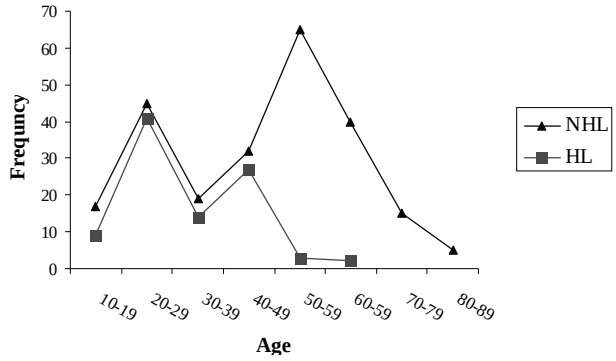

Fig. 1. Bimodal age distribution in HL and NHL.

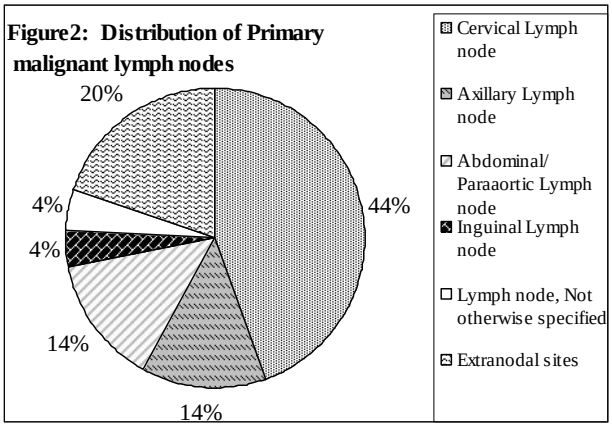

Fig. 2. Distribution of primary malignant lymph nodes.

Accompanied with lymphadenopathy, patient usually complained low grade fever, fatigue, weight loss and abdominal fullness. Physical and clinical findings clearly demonstrated the situation of patient at the time of presentation and it was obvious that most of the victim were suffering from B symptoms (Table II). Fine needle aspiration cytology established the initial diagnosis and surgical resection of lymph node finally confirmed the subtype and cell surface marker by histopathology and immunohistochemistry analysis. Among HL, rate of occurrence of mixed cellularity was highest with 66.7%, and only 22 cases of nodular sclerosis (23%) were identified. In NHL, diffuse large B cell pattern was widespread with 37% cases whereas B cell non Hodgkin's lymphoma exhibited by 41 patients (17%). seventeen patients each of follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) were reported and account for 7% each. Other less common variant included anaplastic large cell lymphoma, lymphoblastic lymphoma and large cell lymphoma.

Table II.- Clinical manifestation of Lymphoma

Physical Signs	HL		NHL	
	Cases (n)	% age	Cases (n)	% age
Fever	96	100	163	68.4
Fatigue	86	89.5	215	90.3
Sweating	64	66.7	157	66
Weight loss	96	100	221	92.8
Abdominal bloating	75	78	192	80.6
Change in bowel habit	64	66.7	140	58.8
Constipation	21	22.2	41	17.2
Vomiting	21	22.2	46	19.3
Difficulty in urine	11	11.5	41	17.2
Loss of appetite	64	66.7	203	85.3
Red patch on skin	21	22.2	99	41.5
Itchy skin	21	22.2	87	36.6
Lymphadenopathy	96	100	238	100
Splenomegaly	32	33.3	29	12.2
Hepatomegaly	32	33.3	46	19.3
Ascites	21	22.2	17	7.1
Pleural effusion	-	-	23	9.7

One interesting finding of the study was that 10% cases of HL and 12.2% cases of NHL had no further subtypes (Table III). This may represent negligence either in surgical resection/specimen collection or in histopathology evaluation. In some cases, histopathology mentioned WHO grade but most of the cases were without grading so cell nature became ambiguous and was difficult to assess whether it was aggressive or indolent. Further work up, including computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone marrow biopsy, was performed to formulate the staging and extent of disease. Twenty seven cases of HL presented with stage I while 10 and 16 patients were in stage II and IV, respectively. Stage III had higher frequency as 44% cases were identified with

stage III. On the other, in NHL, fifty three cases were reported with stage I disease whereas 32 and 45 cases presented with stage II and III respectively. Stage IV was dominant in NHL with 108 cases. The comparison between different stages of HL and NHL showed that stage III was dominant in HL and stage IV in NHL. Stage I lied side by side in both types (Fig. 3). According to SEER summary stage, stage I and II represent local and regional disease respectively while Stage III and IV symbolize for distant metastasis.

Table III.- Histopathology of Hodgkin's and Non Hodgkin's lymphoma.

Type	WHO classification	Cases (n)	% age
HL	Mixed cellularity	64	66.6
	Nodular sclerosis	22	23
	Hodgkin's Lymphoma, NOS*	10	10.4
NHL	Diffuse large B cell lymphoma	90	37.8
	B cell Non Hodgkin's Lymphoma	41	17.2
	Anaplastic large cell lymphoma	13	5.5
	Lymphoblastic lymphoma	8	3.4
	Follicular lymphoma	17	7.1
	Small lymphocytic lymphoma/chronic lymphocytic leukemia	17	7.1
	T cell rich B cell lymphoma	6	2.5
	Large cell NHL	12	5.0
	Diffuse most likely T cell lineage	3	1.3
	Lymphoplasmacytic lymphoma	2	0.84
	Non Hodgkin's Lymphoma, NOS	29	12.2

*NOS: not otherwise specified

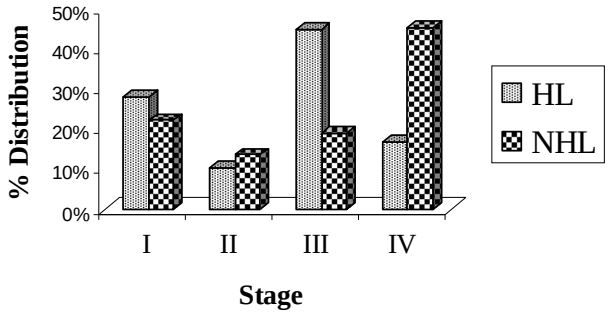

Fig. 3. Distribution of staging in HL and NHL

DISCUSSION

Lymphoma like the other neoplasms shows variation in clinical and demographic presentation. The patients present in the study belong to different geographic and ethnic groups and show evidence of different kinds of lymphoma. This may be associated with certain occupational hazards like exposure to chemicals such as benzene and fertilizers etc. The residential area of patient may have extreme or frequent exposure to pesticides and herbicides. The present study shows the incidence of NHL greater than HL with approximate 2.5:1. This frequency is also affected by age as the study shows that people who develop HL are between 20-30 years of age. On the contrary, victims of NHL are young as well as aged people. Moreover, males are more susceptible than female. This pattern is validated by the previous study (Aziz *et al*., 1999) but no reason was yet established. Age distribution demonstrate bimodal pattern in NHL where first peak lies 20-29 years and second peak involve 40-70 years. HL shows the same pattern with one peak at 20-29 years and second at 40-49 years. These findings are consistent with previous study (Yahalom and Straus, 2008; Horner *et al.*, 2008). The process of aging which contribute to health deterioration may explain this type of distribution. Lymphoma occurs when genes associated with programmed cell death (apoptosis) are irregular, and the lymphocyte's apoptosis response is interrupted. Consequently, the lymphocytes do not die but rather continue to proliferate and circulate causing disease and possible death. The clinical presentation of NHL and HL is also very typical. Lymphadenopathy is a common sign of benign and malignant disorder (Olu-Eddo and Ohanaka, 2006). All HL patients present with single chain of cervical lymph node with no disseminate involvement of other lymph nodes but rather directly engross bone marrow. On the contrary NHL cases present with cervical, Intra abdominal and extranodal sites as well. Most of the cases present with more than one nodal site involvement. There is also a common pattern of diffuse extranodal association and in 20% cases extranodal sites are primary sites involving lymph nodes as secondary sites. Ascites, pleural effusion and focal defect in spleen are also frequent. These all findings affect the staging and extent of disease. In our country the trend to go for regular check up is very low and usually self medication prevent people to go for proper examination so most of the patients are diagnosed when they develop metastasis in more

than one secondary site. Hence 45% patients under study were diagnosed with stage III and IV in HL and NHL respectively where prognosis is very poor and rate of survival become very low. Staging can be related to age because in late age the immunity continues to decrease and body become more susceptible to disease. Hence disease spread rapidly consequences to advance stage. As in advance stage, response to treatment is poor and chances of survival decline so it burdens health budget.

Unfortunately, pathology reports were lacking of WHO grade thereby making prediction about cell nature, whether aggressive or indolent, more difficult. According to 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. 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, lymphoid infiltrates in extra nodal sites, and neoplasm containing lymphocytes (Al-Mobeireek *et al*., 2002; Song *et al*., 2007).

Recent advances attempting at increasing the specificity of FNAC by combining it with immunoflow cytometry (IFC) and immuno-histochemistry (IHC), have proven unsuccessful for certain lymphomas and excisional biopsy is still generally recommended (Mayall *et al*., 2003). Histopathology, cytology and immunohisto-chemistry analysis set the morphological variations in lymphoma. Our study reveals most common variant in NHL is B cell NHL (17%) followed by Diffuse large B cell lymphoma (DLBCL) (38%) while mixed cellularity is dominant entity in HL rather than Nodular sclerosis. An important finding is that 12% cases of NHL and 10% cases of HL have no further specification of type and designated as not otherwise specified.

Stage III and IV are dominating in patients diagnosed with HL and NHL, respectively. This delayed diagnosis reveals unawareness of the importance of regular medical check up in general public of the region. Patients presenting with late stage diagnosis too have poor prognosis that may have economic and social impacts by increasing the burden on health care budget and their families. Health awareness, both for physicians and general population, is required on priority basis.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Mr. Tariq Bashir, Principle Scientific Officer, Institute of Nuclear Medicine and Oncology, Lahore for his cooperation in data collection. The authors are highly obliged Higher Education Commission of Pakistan for providing financial assistance for the study.

DECLARATION OF INTEREST

It is hereby informed that the article entitled, “Incidence and clinical manifestation of lymphoma in central Punjab”, submitted by Ms**.** Tamseela Mumtaz, Dr. Nabila Roohi and Professor Dr. M. Waheed Akhtar for publication in your journal is (i) neither a duplicate publication nor any part of the work is submitted elsewhere, (ii) there are no conflicts relating the manuscript, (iii) the study is funded by Higher Education Commission of Pakistan vide letter No.17-5-4(bm4-093) HEC/Sch/ 2007 dated January 02, 2008 and (iv) the manuscript has been read by all authors, fulfills the requirements for authorship, and represents the original work of the authors.

REFERENCES

ABRAMSON, J.S. AND SHIPP, M.A., 2005. Advances in the biology and therapy of diffuse large B-cell lymphoma: moving toward a molecularly targeted approach**.** *Blood***,** **106**: 1164-1174.

AL-MOBEIREEK, A.F., ARAFAH, M. AND SIDDIQUI, N., 2007. An African male with cough, hemoptysis, weight loss and hypercalcemia: TB or not TB? *Eur. Respir. J*., **20:** 1060–1063.

ARMITAGE, J.O., 2005. Staging non-Hodgkin lymphoma. *CA Cancer J. Clin*., **55:**368–376.

AZIZ, Z., REHMAN, A., AKRAM, M. AND SAEED, A.,

1999. Non-Hodgkin's Lymphoma in Pakistan: A Clinicopathological Profile of 175 Patients. *J. Pakistan med. Assoc.,* **49**: 11.

FREDERICK, L.G. AND DAVID, L.P., 2000. *American Joint Committee on Cancer*, American Cancer Society - 2002 - AJCC staging manual 2000. Sixth edition. Springer link.

FRIEDBERG, J.W., MAUCH, P.M., RIMSZA, L.M. AND FISHER, R.I., 2008. Non-Hodgkin's lymphomas. In: *DeVita, Hellman, and Rosenberg's cancer: Principles and practice of oncology* (eds. V.T. DeVita, T.S. Lawrence and S.A. Rosenberg), 8th ed. Lippincott Williams & Wilkins, Philadelphia, Pa, pp. 2278-2292.

GHOBRIAL, I.M., MCCORMICK, D.J., KAUFMANN, S.H., LEONTOVICH, A.A., LOEGERING, D.A., DAI, N.T., KRAJNIK, K.L., STENSON, M.J., MELHEM, M.F., NOVAK, A.J., ANSELL, S.M. AND WITZIG, T.E., 2005. Proteomic analysis of mantle-cell lymphoma by protein microarray. *Blood*, **1; 105**: 3722-30.

GRIBBEN, J.G. AND LACASCE, A.S., 2005. Clinical manifestations, staging, and treatment of non-Hodgkin's lymphoma. In: *Hematology: Basic principles and practice* (eds. R. Hoffman, E.J. Benz, S.J Shattil, B. Furie, H.J. Cohen, L.E. Silberstein, and P. McGlave), 4th ed. Elsevier, Philadelphia, Pa: pp. 1397-1419.

HORNER, M.J., RIES, L.A.G., KRAPCHO, M., NEYMAN, N., AMINOU, R., HOWLADER, N., ALTEKRUSE, S.F., FEUER, E.J., HUANG, L., MARIOTTO, A., MILLER, B.A., LEWIS, D.R., EISNER, M.P., STINCHCOMB, D.G. AND EDWARDS, B.K., 2008. *SEER Cancer Statistics Review, 1975-2006*, National Cancer Institute.. Bethesda, MD.

JAFFE, E.S. AND PITTALUGA, S., 2005. The pathologic basis for the classification of non-Hodgkin's lymphoma. In: *Hematology: basic principles and practice* (eds. R. Hoffman, E.J. Benz, S.J. Shattil, B. Furie, H.J. Cohen, L.E. Silberstein and P. McGlave), 4th ed. Elsevier, Philadelphia, Pa, pp. 1379-1396.

MAYALL, F., DARLINGTON, A. AND HARRISON, B., 2003. Fine needle aspiration cytology in the diagnosis of uncommon types of lymphoma. *J. clin. Pathol.,* **56:** 821–825.

OLU-EDDO, A.N. AND OHANAKA, C.E., 2006. Peripheral lymphadenopathy in Nigerian adults. *J. Pakistan med. Assoc.*, **56:** 405–408.

PHELAN, E., LANG, E., GORMLEY, P. AND LANG, J., 2007. Kikuchi-Fujimoto disease: a report of 3 cases. *Ear Nose Throat J.*, **86**: 412–413.

ROSEN, S.T., WINTER, J.N. AND GORDON, L.I., 2008. Non-Hodgkin lymphoma. In: *Cancer management: A multidisciplinary approach* (eds. R. Pazdur, L.D. Wagman, K.A. Camphausen and W.J. Hoskins), 11th ed. CMPMedica, Lawrence, KS, pp.719-774.

SONG, J.Y., CHEONG, H.J., KEE, S.Y., LEE, J., SOHN, J.W. AND KIM, M.J., 2007. Disease spectrum of cervical lymphadenitis: analysis based on ultrasound-guided core-needle gun biopsy. *J. Infect.,* **55:** 310–316.

WILSON, W.H. AND ARMITAGE, J.O., 2008. Non-Hodgkin's Lymphoma. In: *Abeloff's clinical oncology* (eds. M.D. Abeloff, J.O. Armitage, J.E. Niederhuber, M.B. Kastan and W.G. McKenna). 4th ed. Elsevier, Philadelphia, Pa, pp. 2371-2404.

WU, G. AND KEATING, A., 2006. Biomarkers of potential prognostic significance in diffuse large B-cell lymphoma. *Cancer*, **106**: 247-257.

YAHALOM, J. AND STRAUS, D., 2008. Hodgkin's lymphoma. In: *Cancer management: A multidisciplinary approach* (eds. R. Pazdur, L.D Wagman, K.A. Camphausen and W.J. Hoskins,) 11th ed. C M P Medica, Lawrence, KS, pp. 697–717..

YOUNG, J.L.JR., ROFFERS, S.D., RIES, L.A.G., FRITZ, A.G. AND HURLBUT, A.A., 2001. *Surveillance epidemiology and end results. SEER Summary Staging Manual- 2000:* Codes and Coding Instructions, National Cancer Institute, NIH Pub. No. 01-4969, Bethesda, MD,

(Received 8 April 2012, revised 30 August 2012)