Original Article

Malignant Lymphomas

# Incidence of Malignant Lymphomas in Balochistan

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## ABSTRACT

**Background:** Traditionally lymphomas are classified into Hodgkin's disease (HD) and Non Hodgkin's lymphoma (NHL) depending upon histo-pathological evidence on biopsy taken from an enlarged lymph node. Delayed diagnosis in lymphoma deteriorates the health eminence resulting in poor outcome.

**Objectives:** The aim of the study is to estimate the incidence and clinical presentation of malignant lymphomas in Balochistan.

**Study Design:** Prospective Study

**Place and Duration of Study:** This study was carried in the Department of Radiotherapy & Oncology, Bolan Medical Complex Hospital, Quetta from June, 2006 to May, 2012

**Materials and Methods:** A total of 263 newly diagnosed patients of both types of lymphoma from different parts of Balochistan were registered in Bolan Medical Complex Hospital in Department of Radiotherapy & Oncology. Followed by histopathology, WHO classification and Ann Arbor staging was done to assign subtype and extent of disease.

**Results:** It was found that the incidence of Non Hodgkin's lymphoma a (64.7%) was greater than Hodgkin's disease (35.2%) and both present bimodal distribution in age. Male patients dominate female patients in both cases (2.5:1). Lymph-adenopathy of cervical region was primary site in 44 % of cases while 27.6 % were extra nodal. Histopathology shows 57.4 % mixed cellularity variant in Hodgkin's lymphoma and 25.5% diffuse B cell pattern in Non Hodgkin's lymphoma. Ann Arbor staging reveals that 3.4% cases present with stage I and 64.5% show stage IV.

**Conclusion:** To conclude Non Hodgkin's lymphoma is two times more frequent than Hodgkin's lymphoma with greater male contribution. Due to delayed diagnosis resulted in late stage presentation ,health awareness is needed for physicians and general population for availability of patients at a due time for management.

**Key Words:** Hodgkin's lymphoma, Non Hodgkin's lymphoma, Lymph-adenopathy.



## INTRODUCTION

Lymphomas are group of disorders caused by malignant lymphocytes that accumulates in lymph nodes and cause the characteristic feature of lymph-adenopaty. Occasionally, they may spill over in blood or infiltrate organs outside the lymphoid tissue [1]. Lymphatic organs play an important part in the immune system, having a considerable overlap with the lymphoid system. Lymphoid tissue is found in many organs, particularly the lymph nodes, and in the lymphoid follicles associated with the digestive system. Lymphoid tissues contain lymphocytes, but they also contain other types of cells for support [2]. The system also includes all the structures dedicated to the circulation and production of lymphocytes, which includes the spleen, thymus, bone marrow, and the lymphoid tissue associated with the digestive system[3]. 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, 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 of origin as it strappingly affects treatment modality. The primary site may be nodal when malignant cells originate from lymph nodes and is extra nodal when develop from the organs other than lymphatic system such as gastrointestinal tract, hypochondriam, Para-nasal sinuses, central nervous system . Lymphoma may invade the nearby organs involving extra nodal sites and vice versa [4].

Traditionally lymphomas are classified into Hodgkin's disease (HD) and Non Hodgkin's lymphoma (NHL) depending upon histo-pathological evidence on biopsy taken from an enlarged lymph node. Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage and has characteristics Read Sternberg cells having large, abundant cytoplasm, double or multiple nuclei with its distinctive clinical features [5]. Since there are so many different types of lymphomas, its classification is very complicated [6]. Many of these subtypes look similar but they are functionally quite different and respond to different types of therapies with different probability of cure [7].

Diffuse large B cell Lymphoma is most common and is potentially curable while mantle cell lymphoma is unique subtypes B cell lymphoma and is potentially incurable [4,8,9]. Due to the varied clinical picture, many patients are misdiagnosed and treated for diseases like tuberculosis[10]. Sometimes, 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 [11]. The first sign of lymphoma is painless enlarged lymph nodes accompanying fever for more than 3 days. Usually patient presents with low grade intermittent 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. High grade lymphoma has cells and multiply rapidly hence aggressive in nature while low grade lymphoma cells look much similar to normal cells, multiply slowly and are indolent. Lymphomas are also categorized on the basis of tumor burden for appropriate treatment. The Ann arbor staging system 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 [5].

The aim of this study is to evaluate the incidence of malignant lymphomas and its extent at the time of presentation and to promote health awareness in population.

## MATERIALS AND METHODS

In this prospective study, 263 newly diagnosed patients of both types of lymphoma from different parts of Balochistan, were registered in Bolan Medical Complex Hospital, Quetta, in Department of Radiotherapy & Oncology, from June, 2006 to May 2012. The study includes patients of all ages and sexes. Exclusion criteria from the study were the patients having chronic lymphocytic leukemia and patients with viral hepatitis. Informed consent was obtained from individual patients for collecting demographic and disease data on pre-designed questionnaire. Initial laboratory evaluation included complete blood count, erythrocyte sedimentation rate, serum electrolytes and urine analysis. Further investigation includes biochemical tests like renal function test, liver function test, total proteins and blood urea, serum creatinin, specific tests such as lactate dehydrogenate and $B_2$ micro globulin 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 ultra sonogram, magnetic resonance imaging, computer tomography 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.

## RESULTS

Two hundred and sixty nine diagnosed cases of lymphomas were included in this prospective study, out of which 169(71%) cases belonged to NHL with male to female ratio 1.5:1 while 94 (29%) cases were diagnosed having HD with male to female ratio 2:1. Demographics (Table.1) showed that in HL group 56 (60%) were males and 38 (40.4%) patients were females. The patients were divided in two groups, age<40 years consist of 62 (65.9%) patients and age ≥ 40 years consist of 32 (34%) patients. In NHL group, out of 169 (64.9%) patients ,32 (34%) patients were ≥ 40 years. In NHL group, out of 169(64.2) patients, the 123 (172.7) patients were male and 46 (27.2) patients were female. Graphical representation of frequency of age exhibited bimodal distribution, where the first peak appears between 20-29 years, both HD and NHL whereas, in HL the second larger peak stuck between 50-59 years. On general examination, lymph-adenopathy was the commonest finding and 100% patients presented with enlarged lymph node of any site. The most frequent primary sites were cervical lymph nodes (41%). It was also observed that incidence of malignant site was also very high (28%), so was the abnormal lymphocyte growth outside the lymphatic system (Fig.1). All extra nodal cases were Non Hodgkin lymphomas. Accompanied with lympha-denopathy, 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 victims were suffering from B symptoms (Table.1). 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 immuno-histochemistry analysis. Among HD, rate of occurrence of mixed cellularity was highest with 77.5%, and only 18 cases of nodular sclerosis (22.5%) were indentified. In NHL, diffuse large B cell pattern was widespread with 45% cases whereas B cell Non Hodgkin's lymphoma exhibited by 23 patients (13%),seventeen patients each of follicular lymphoma and small lymphocytic lymphoma (SLL) ,7 % each were reported (Table.2). Other less common variant included anaplastic large cell lymphoma, lymphoblastic lymphoma and large cell lymphoma.

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. Eight (8.5%) cases of HL presented with stage I while 12 (12.7%) in stage II and 16 (17%) patients were in stage III and 58 (61.7%) patients were in stage IV, respectively. Stage IV had higher frequency as 61.7% cases were identified with stage IV. One the other, in NHL, 6 (3.5%) cases were stage I disease whereas 19(11.2%) and 45(26.6%) cases presented with stage II and III respectively. Stage IV was dominant in NHL with 109 (64.4%) 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.2), according to SEER summary stage, stage I
and II represent local and regional disease respectively while stage III and IV symbolized for distant metastasis..

**Table No. 1: Characteristics of 263 patients Presenting with(HL 94 cases and NHL 169 cases).**

| | HL | | NHL | |
|---|---|---|---|---|
| **Characteristics** | No | (%) | No | (%) |
| Sex | | | | |
| Male | 56 | 60 | 123 | 72.7 |
| Female | 38 | 40.4 | 46 | 27.2 |
| Age | | | | |
| ≤4 yr | 62 | 65.9 | 61 | 36 |
| ≥4 yr | 32 | 34 | 108 | 63.9 |
| **Ann Arbor Stage** | | | | |
| I | 08 | 8.5 | 06 | 3.5 |
| II | 12 | 12.7 | 19 | 11.2 |
| III | 42 | 24.8 | 45 | 26.6 |
| IV | 32 | 34 | 109 | 64.4 |
| **Presentation** | | | | |
| Nodal | 68 | 72.3 | 128 | 75.7 |
| Extra nodal | 26 | 27.6 | 41 | 24.2 |
| Symptoms | | | | |
| Fever | 78 | 82.9 | 134 | 79.2 |
| Weight loss | 69 | 73.4 | 112 | 66.2 |
| **Lymphomatous involvement** | | | | |
| Spleen | 72 | 76.5 | 104 | 61.5 |
| Bone Marrow | 31 | 32.9 | 42 | 24.8 |
| Liver | 48 | 51 | 71 | 42.0 |
| GIT | 26 | 27.6 | 36 | 21.3 |
| CNS | 02 | 2.1 | 03 | 1.7 |
| Pleural effusion | 08 | 8.5 | 11 | 6.5 |
| Asities | 10 | 10.6 | 16 | 9.4 |
| **LDH** | | | | |
| 1. Normal | 30 | 31.9 | 42 | 24.8 |
| 2. Abnormal | 58 | 61.7 | 113 | 66.8 |
| 3. Not known | 06 | 3.5 | 12 | 7.1 |
| **Extranodal involvement** | | | | |
| 1 Site | 36 | 21.3 | 45 | 26.6 |
| 2 or > 2 sites | 51 | 30.1 | 109 | 64.4 |
| Not known | 7 | 4.1 | 13 | 7.6 |

**Table No. 2: Different types of NHL cases**

| Type | WHO classification | Cases | %age |
|---|---|---|---|
| HL | Mixed callularity | 54 | 57.4 |
| | Nodulr sclerosis | 24 | 25.5 |
| | Nodular lymphocyte | 10 | 10.6 |
| | Predominanat Lymphocyte rich | 06 | 6.3 |
| NHL | Diffuse large B cell Lymphoma | 85 | 37.8 |
| | Small Lymphocytic Lymphoma | 40 | 17.2 |
| | Folicular Lymphoma | 15 | 8.8 |
| | Mantle cell Lymphoma | 13 | 7.6 |
| | Anaplastic large T-cell Lymphoma | 10 | 5.9 |
| | Lymhoblastic Lymphoma | 8 | 4.7 |
| | Peripheral T-Cell Lymphoma | 5 | 2.9 |

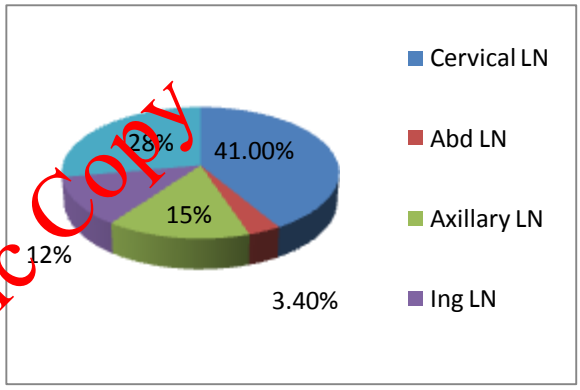


**Figure No.1: Distribution of Malignant lymph nodes in NHL.**

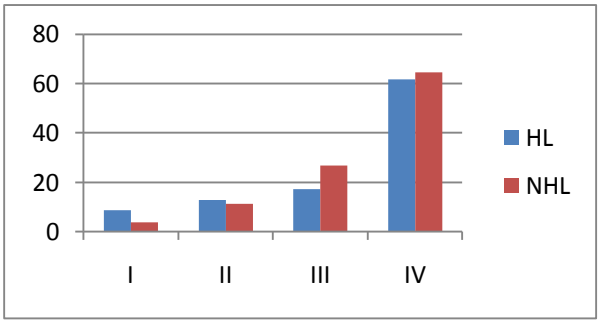


**Figure No.2: Staging in HL and NHL.**

## DISCUSSION

Lymphoma is the most common form of hematological malignancy in the developed world. With addition of life style, malignant lymphoma is increasing in developing countries. Malignant lymphomas accounts for 5.3% and 55.6% of all blood cancers. According to the National Institute of Child Health, lymphomas account for about five percent of all cases of cancer in the United States, and Hodgkin's lymphoma in

particular accounts for less than one percent of all cases of cancer in the United States.

The patients present in the study belong to different geographic and ethnic groups and show evidence of different kinds of lymphoma. The present study shows the incidence of NHL greater then HL with approximate 2.5:1. This frequency is also affected by age as the study shows that people who develop HL are between 30-40 years of age. On the contrary, victims of NHL are young as well as aged people. Moreover, males are more susceptible then female. This pattern is validated by the previous study but no reason was yet established. Age distribution demonstrate bimodal pattern in NHL where first peak lies 30-40 years and second peak involve 41-70 years. HL shows the same pattern with one peak at 3-40 years and second at 41-49 years. These findings are consistent with previous studies [12,13]. 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 lymphocytes 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. Lymph-adenopathy is a common sign of beginning of malignant disorders [14]. 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 extra nodal sites as well. Most of the cases present with more than one nodal site diffuse extra nodal association and in 20% cases extra nodal sites are primary sites involving lymph nodes as secondary sites. Ascites, pleural effusion and focal defect in spleen and GIT involvement are also frequent. These all findings effect 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 to go for examination, so most of the patients are diagnosed when they develop metastasis in more than one secondary site. Hence 45% under study were diagnosed with stage III and IV in HL and NHL respectively where prognosis is very poor and rate of survival is low because in late age the immunity continues to decrease and body rapidly consequences to advance stage. As in advance stage, response to treatment is poor and chances of survival decline so it burdens health budget.

According to WHO, morphological diagnosis of NHL relies on cytological details, although the development of new technologies has helped to define several NHL tend to be sclerotic and diagnosis is possible only with excisional biopsy [15,16]. Fine needle aspiration cytology (FNAC) though minimally invasive, produces suboptimal material and reveals scanty neoplastic cells. Presence of lymphoid cell 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 site, and neoplasm containing lymphocytes [17].

Recent advances attempting at increasing the specificity of FNAC by combining it with immune flowcytometry (IFC) and immune-histochemistry (IHC), have proven unsuccessful for certain lymphomas and excisional biopsy is still generally recommended[18]. Histopathology, cytology and immuno-histochemistry analysis set the morphological variations in lymphoma. Our study reveals most common variant lymphoma Diffuse Large B Cell Lymphoma (DLBCL) (38%), since DLBCL is heterogeneous, CNS prophylaxis by adding ritoxumab in chemotherapy is promising [19,20], 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 . 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.



## CONCLUSION

To conclude Non Hodgkin's lymphoma is two times more frequent than Hodgkin's lymphoma with greater male contribution. Due to delayed diagnosis resulted in late stage presentation ,health awareness is needed for physicians and general population for availability of patients at a due time for management.

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