RESEARCH ARTICLE

Signs, Symptoms and Complications of Non-Hodgkin's Lymphoma According to Grade and Stage in South Iran

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Abstract

Background: Non-Hodgkin's lymphoma (NHL) is a heterogeneous type of neoplasm of the lymphatic system. To have a more accurate and early diagnosis we need to know signs, symptoms and complications of lymphoma in early stages besides pathology and immunohistochemistry. Materials and Methods: This prospective study included 110 cases of NHL that were followed since February 2012 till November 2013. Biopsies were taken from all the patients besides bone marrow study. Signs and symptoms were categorized into "B" symptoms, general, lymphadenopathy and extranodal involvement and we compared the frequencies by stage and grade. Results: Of 110 cases, 88.9% had B-cell and 11.1% T-cell type with mean age 48.5±18.6 years. "B" symptoms and lymphadenopathy were more common in men. Cervical lymphadenopathy was the most common sign (44.8%). and hematologic, bone marrow, bone and neurologic lesions were the most common complications. All complications were more common in males. "B" symptoms were seen mostly in stage III, general signs and symptoms in stage IV, and lymphadenopathy in stage II. Intermediate grade was also the most common in all signs and symptoms. In this study 12 (10.9%) patients had relapse, with neurologic and bone marrow as the most common sites of tumor recurrence. Conclusions: There is a meaningful relationship between male gender for NHL and anemia that can be due in part to higher incidence of bone marrow involvement and stage IV disease in male cases. We also found a strong relationship between low grade NHL and age. On the other hand extranodal involvement is more common in female groups.

Keywords: Non-Hodgkin's lymphoma - grade - stage - signs - symptoms

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Introduction

Non Hodgkin Lymphoma (NHL) is a heterogeneous type of neoplasm related to lymphoreticular system that its prevalence during the twenty years ago has increased. In 2010, NHL was diagnosed as the sixth most common cancer and the eighth common cause of death due to cancers among men and women while presentation of NHL in men was 50% more than women (Johnston et al., 2010).

Clinical manifestations of NHL are very variable. Most common clinical presentations include: "B" symptoms (fever, night sweating and weight loss), anorexia and lymphadenopathy especially in cervical, axillary and inguinal regions. Also the pressure effect of the enlarged lymph node is a common manifestation. Some patients may present with extranodal involvement without lymphadenopathy like gastrointestinal bleeding due to gastric lymphoma. Some of the other presentations include splenomegaly, bone pain and unreasonable fatigue. However sometimes patients are asymptomatic or they are diagnosed accidentally during the work ups for another reason. Considering common complications after chemotherapy, we can mention to nausea, vomiting, constipation, hair loss, lack of energy, neutropenia and infectious diseases. NHL may also be accompanied by some complications that are not related to treatment such as skin complications, metabolic and neuropathy (Zelenetz et al., 2011, Bolukbas et al., 2014). Prognosis and therapy depend not only on stage but also on the pathologic features, grade and clinical parameters that reflect tumor bulk and kinetics (Huff et al., 2006).

Advances in treatment and different chemotherapy protocols has increased the number of long-term survivors, so identification of late effects of lymphoma and its treatment has a critical value in long term follow ups of the patients (Ng et al., 2011).Treated patients of NHL are at risk of secondary malignancies such as acute myeloid leukemia, cancer of bladder, lung cancer. Other common complications caused by treatment include infertility, neuropathy, renal failure and lung fibrosis. Gastrointestinal and cardiac involvement can cause complications including obstruction or pericardial effusion and tamponade (Ng et al., 2011).

Non-Hodgkin's lymphoma includes 8.4% of all cancers in Iran and the most common type is high

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grade lymphoma at diagnosis (Hingorjo et al., 2008). Considering the high prevalence and late diagnosis we need more research to determine and diagnose the disease sooner when treatment is much more effective. On the other hand variable clinical presentations of lymphoma can cause delay in diagnosis till the end stages. To have a more accurate and early diagnosis we need to know signs, symptoms and complications of lymphoma in early stages besides pathology and immunohistochemistry studies, so that physicians will be able to diagnose the disease earlier and increase the chance to treat this malignant disease. In this research we studied Non-Hodgkin lymphoma which includes B-Cell and T-cell types with different subtypes based on pathology and immunohistochemistry studies.

Materials and Methods

This is a prospective study including 110 cases of NHL that were followed since February 2012 till November 2013. The patients were collected from hematologic wards and two outpatient clinics in Shiraz University of Medical Sciences.

Based on the sites of involvement, biopsies were taken for pathologic and immunohistochemistry studies in all the patients besides bone marrow biopsies during staging process. Those patients that had a non-lymphoma or undetermined histopathological findings or cases with diagnosis of Hodgkin's disease were excluded from our study. All patients included in this study had pathologically proven NHL.

A complete physical exam was done at presentation and relapse for each patient. Signs and symptoms were categorized into four groups of "B" symptoms, general signs and symptoms, lymphadenopathy and extranodal involvement. General signs and symptoms included malaise, fatigue, anorexia and decreased appetite, temporal wasting, generalized edema and body pain. Classification of NHL was done based on the last WHO classification method (fourth edition in 2008) and grade of disease was determined in pathologic studies too.

In order to find the stage of lymphoma, all new cases went through a complete physical exam, thoracic, abdominal and pelvic CT scan and also bone marrow biopsy. Based on the signs and symptoms implying probable site of involvement some patients had extra work ups such as brain CT scan and lumbar puncture for neurologic manifestations or endoscopic study and biopsy for those who had gastrointestinal signs and symptoms at presentation or relapse.

Some laboratory evaluations including: CBC, Chemistry, ESR, LDH, coagulation profiles, liver function tests and also viral markers of HBV, HCV and HIV were done at presentation and relapse. High LDH level was considered more than 500 which was classified into 3 groups of 500-1000, 1000-1500 and more than 1500. Age of the patients were divided into 4 groups of less than 19, 20-39, 40-59 and more than 60 years.

Statistical analysis

All the data were gathered in a patient information form for each of the cases, coded and recorded in 2010 excel software and finally analysis was done by using SPSS 18. Statistical methods are explained below. Descriptive analysis determined the mean, median, standard deviation and frequency of the variables. Chi square test, ANOVA test and independent sample t-test were also used for this analysis.

Results

Out of 110 cases of NHL that were included in this study, majority of patients were B-Cell 96 (88.9%) and 12 (11.1%) cases were T-cell type. Mean age of the patients was 48.48±18.55 years with range of 17-84 years. By comparing the pathologic reports, we discovered there is a significant difference between the ages of patients who present with NHL at low grade in contrast with intermediate and high grades. Those patients who are diagnosed at low grade are mostly older than the patients at intermediate grade (P: 0.031) and high grade (0.003). (Figure 1)

"B" symptoms and lymphadenopathy were more common in men compared to women. .Lymphadenopathy that is a very common presentation was found in 53 cases (48.6%) clinically and after further investigations and imaging studies 58(53.2%) cases were detected with lymphadenopathy. Cervical lymphadenopathy was the most common site accounting for 44.8% of lymphadenopathies. (Table1)

As the patients were followed their complications were detected and it was shown that hematologic, bone marrow, Bone and neurologic involvements were the most common complications with frequencies of 72.2%, 13.8%, 11.9%, 11% respectively.

The only complication that showed a reverse male to female ratio i.e. a ratio less than 1 was SVC syndrome which was seen in 2 female and 1 male.

In this study extranodal stage was the most frequent pattern seen between NHL patients (28%), followed by stage II (27.1%) and stage IV (20.6%).

"B" symptoms were seen mostly in stage III, General signs and symptoms in stage IV, lymphadenopathy in stage II. However the most common presentation in stages I to III was lymphadenopathy and in stages IV and E, was extranodal signs and symptoms. Intermediate grade was also the most common grade in all signs and symptoms and extranodal signs and symptoms were the most common

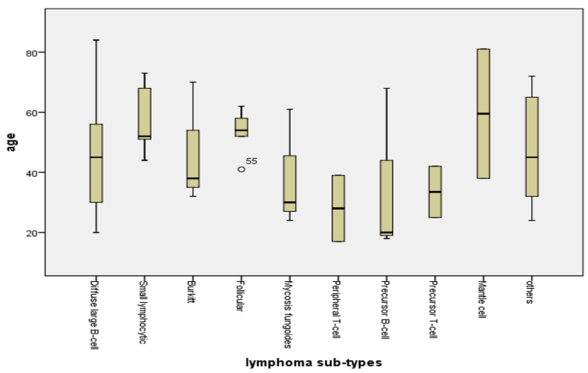

Figure 1. Lymphoma Age Distributions Categorized by Pathologic and Immunohistochemichal Sub-types

presentation in all of the three grades. (Table 2)

Most of the complications were accompanied by stage IV except the thrombosis, Airway and lung, skin and post chemotherapy or radiotherapy complications which were more common in stage II, SVC syndrome was seen in stage I as frequent as stages II and IV .

Splenomegaly was seen with the same frequency in stages II, III and IV however it was the most frequent symptom in stage III after hematologic abnormalities accounting for 15.8% of stage III cases. In this study 59.6 % patients presented with extranodal signs and symptoms that had a wide spectrum with GI presentations at the top of the list. 32.3% of the cases with extranodal involvement showed "B" symptoms at presentation too. Finally hematologic and GI complications were mainly seen in extranodal stage and they were the most common type of complications in extranodal stage (Table 3).

Table 1. Demographic Features of Patients

Patients Characteristics	Number and percent
Age years , Mean±SD	48.48±18.55
Range	17-84
Median	49.5
Male/Female Ratio	1.62
B Cell	96 (88.9%)
T Cell	12 (11.1%)
signs and symptoms	
"B" symptoms	39 (35.8%)
General	32 (29.4%)
Lymphadenopathy	53 (48.6%)
Extranodal site involvement	65 (59.6%)
Site of Lymphadenopathy	
Cervical	26(37.14%)
Axillary	12(17.14%)
Mediastinum	9(12.85%)
Para-aortic	5(7.14%)
Inguinal region	13(18.57%)
Other site†	5(7.14%)
Staging	
I	7(6.5%)
II	29 (27.1%)
III	19 (17.8%)
IV	22 (20.6%)
Extranodal	30 (28%)
Grading	
Low grade	23 (21.1%)
Intermediate	63 (57.8%)
High(very aggressive)	23 (21.1%)
Extranodal involvement	
Low grade	12(52.2%)
Intermediate	38(61.3%)
High(very aggressive)	14 (60.9%)
WHO classification	
Diffuse Large B-Cell Lymphoma	45(60%)
Small lymphocytic lymphoma	5(6.7%)
Follicular lymphoma	5(6.7%)
Others*	20 (26.7%)

*Burkitt lymphoma, Mycosis Fungoid, Peripheral T cell lymphoma, Precursor B cell lymphoma, Precursor T cell lymphoma, Mantle cell lymphoma, T cell B cell rich lymphoma, Mucosa Associated Lymphoid Tissue (MALT), T-cell lymphoblastic lymphoma, Anaplastic large cell lymphoma and precursor B cell lymphoblastic lymphoma; † Other site: Hilum of liver, mesenteric lymphadenopathy

Extranodal lymphoma showed a male to female ratio of 1.41 which is 0.21 lower than the overall male to female ratio of NHL. When we restricted the data to the primary extranodal lymphomas this ratio changed to 1.14 and by comparing the extranodal stage between male and female cases it was evident that primary extranodal lymphoma is more common between female group of NHL than the male patients in this study.

Hematologic complication including anemia, leukopenia, thrombocytopenia and hemolysis, was the most common complication in all stages. Patients in stage I showed only complications of hematologic involvement, splenomegaly and SVC syndrome. The second most common complication in stage II was airway and lung complication and in stage III bone marrow involvement and splenomegaly. In stage four and extranodal stage gastrointestinal involvement was the most common symptoms and complications (Table 3).

Pathologic studies and immunohistochemistry results showed the most common pathologic sub-type was diffuse large B-cell lymphoma (DLBCL) accounting for 60% of seventy five cases that had specified pathologic sub-types.

Complications were also classified by pathologic findings. Results showed that B-cell NHL was the most common type that presented with different complications of which DLBCL sub-type was the most frequent between most of the complications. However the "others" group was more common among patients with renal failure, bone marrow involvement and infectious complications.

After clustering the cases based on their pathologic findings, it was seen that hematologic abnormalities were the most common complication in each of the pathological types and sub-types followed by bone and neurologic involvements in B-Cell NHL patients with frequency of 11.6% for each of them while among patients with T-cell NHL, bone and bone marrow involvements were more common with frequencies equal to 16.7% for each. Neurologic complications were more frequent among patients with DLBCL with frequency of 13.3%. Bone involvement, hematologic, Airway and lung complications and bone marrow involvement were the complications seen in small lymphocytic lymphoma patients. Splenomegaly and post radiotherapy or chemotherapy complications

Table 2. Signs and Symptoms by Grade and Stage

Signs and symptoms	*Grade %			Stage %				
	1	2	3	I	II	III	IV	E
"B" symptoms	21.1	55.3	23.7	0	23.7	31.6	21.1	23.7
General	25.8	51.6	22.6	0	20	20	36.7	23.3
Lymphadenopathy	18.9	56.6	24.5	7.5	39.6	32.1	17	3.8
Extranodal	18.8	59.4	21.9	3.1	16.9	3.1	29.7	46.2
Total number (%)	23 (21.10)	63 (57.80)	23 (21.10)	7 (6.50)	29 (27.10)	19 (17.80)	22 (20.60)	30 (28)

apart from hematologic abnormalities were those complications that were seen in patients with follicular lymphoma. In the others group bone complications and bone marrow involvement were the most common after hematologic complication. Bone involvement was seen in small lymphocytic lymphoma, DLBCL, mantle cell lymphoma, precursor T-cell lymphoma and in T cell lymphoblastic leukemia and the most prevalent was small lymphocytic lymphoma. (Table 4)

Laboratory data was also classified based on sex, age, stage, and pathologic findings. In all of the laboratory abnormalities there was a male dominancy except for high ESR level which was significantly more frequent between females than male cases with male to female ratio of 0.71 P (0.002). Between male cases 31.2 % presented with high ESR level while 77.8 % of females had high ESR at presentation.

The relationship between anemia and sex was also meaningful (P 0.024). This showed that anemia occurs more frequently in men compared to female cases of NHL. Of those who had anemia, 71.7% were male and 28.3% were female also 71.7% of male patients with NHL

Table 3. Complications by Grade and Stage

Signs and symptoms	*Grade %			Stage %				
	1	2	3	I	II	III	IV	E
Neurologic	0	90.9	9.1	0	18.2	0	45.5	36.4
Bone	7.7	69.2	23.1	0	7.7	15.4	46.2	30.8
Thrombosis	0	50	50	0	75	0	0	25
Hematologic	22.9	52.9	24.3	7.1	21.4	20	25.7	25.7
Gastrointestinal	14.3	57.1	28.6	0	14.3	14.3	0	71.4
Liver function abnormalities	0	100	0	0	0	0	100	0
Renal function abnormalities	0	100	0	0	50	0	50	0
Airway and lung	11.1	66.7	22.2	0	55.6	22.2	11.1	11.1
Bone Marrow involvement	40	26.7	33.3	0	0	0	100	0
Skin	100	0	0	0	100	0	0	0
Soft tissue involvement	0	50	50	0	25	25	50	0
SVC syndrome	0	66.7	33.3	33.3	33.3	0	33.3	0
Infections	0	50	50	0	0	0	100	0
Post chemotherapy or Radiotherapy	40	40	20	0	60	0	0	40

*E: Extranodal

Table 4. Complications by Pathologic Findings

Complications	Type		Pathologic sub-type %			
	B-Cell	T-Cell	DLBCL*	SLL‡	FL#	Others†
Neurologic	91.7	8.3	66.7	0	0	33.3
Bone	84.6	15.4	50	10	0	40
Thrombosis	100	0	100	0	0	0
Hematologic	88.6	11.4	63.6	4.5	4.5	27.3
Gastrointestinal	85.7	14.3	100	0	0	0
Liver function abnormalities	100	0	-	-	-	-
Renal function abnormalities	100	0	0	0	0	100
Airway and lung	100	0	71.4	14.3	0	14.3
Bone Marrow	86.7	13.3	14.3	14.3	0	71.4
Skin	100	0	0	0	0	100
Soft tissue involvement	75	25	50	0	0	50
SVC syndrome	100	0	50	0	0	50
Infections	100	0	0	0	0	100
Postchemotherapy or Radiotherapy	80	20	50	0	25	25

* Diffuse large B-cell lymphoma ‡Small lymphocytic lymphoma; #Follicular lymphoma †Others: other subtypes of nonhodgkins lymphoma including: Burkit lymphoma, Mycosis Fungoid, Peripheral T cell lymphoma, Precursor B cell lymphoma, Precursor T cell lymphoma, Mantle cell lymphoma, T cell B cell rich lymphoma, Mucosa Associated Lymphoid Tissue (MALT), T-cell lymphoblastic lymphoma, Anaplastic large cell lymphoma and precursor B cell lymphoblastic lymphoma

Table 5. Laboratory Findings by Pathology and Immunohistochemistry and Grade

Laboratory findings	Pathologic sub-type %					Grade %			
	B-Cell	T-Cell	DLBCL	Small lymphocytic	Follicular lymphoma	Others	1	2	3
Leukopenia	100	0	55.6	11.1	11.1	22.2	33.3	53.3	13.3
Anemia	86.4	13.6	62.2	2.7	5.4	29.7	23.3	55	21.7
Thrombocytopenia	86.7	13.3	56.2	6.2	0	37.5	24.1	44.8	31
High ESR	91.3	8.7	58.3	8.3	16.7	16.7	30.4	60.9	8.7
High LDH	90.9	9.1	68.8	6.2	0	25	17.4	56.5	26.1

presented with anemia while only 48.6% of female cases presented with anemia when NHL was diagnosed.

After classifying laboratory findings by sex and stage we found that anemia was the most common finding in male patients while high ESR level was the most frequent finding in female cases. The hematologic abnormalities including leukopenia, anemia, thrombocytopenia and high ESR level were more common in stage IV. Only high serum LDH level showed to be more common in stage III. The most common laboratory finding was anemia in any stages except stage III which showed high LDH level to be at the top. In extranodal stage high serum LDH level was not common.

When we compared laboratory data with pathologic findings it was seen that all of the abnormalities were more common in B-Cell NHL than T-Cell type and serum LDH levels that were more than 1000 were only detected in B-Cell NHL. DLBCL was the most common sub-type in all of the abnormal laboratory findings and intermediate grade was the most common grade seen among the patients with leukopenia, anemia, thrombocytopenia and high serum ESR and LDH levels. On the other hand Anemia, thrombocytopenia and high LDH level were more common in high grade group while leukopenia and high serum ESR level were more commonly seen between low grades. (Table 5)

We detected pleural effusion in six patients at presentation and one patient at relapse. Hematologic abnormalities were the most common complication at presentation which could be due to bone marrow involvement, splenomegaly, anemia of chronic disease and etc. Seventy one cases (73.2%) showed hematologic involvement in this study including pancytopenia, bicytopenia, anemia, leukopenia, thrombocytopenia and also coombs positive hemolysis that occurred in one patient. Some other life threatening complications included methotrexate toxicity, tamponade, SVC syndrome, small bowel (jejunum) perforation, bowel obstruction, acute appendicitis and obstructive jaundice due to mass of pancreas.

We detected 3 cases of the blood born infections in this study. HIV related NHL was found in a 32 years old female with bone marrow involvement that presented at stage IV and high grade with pathologic sub-type of Burkitt lymphoma-leukemia. Hepatitis B virus antigen was positive in a 55 years old man who came with intermediate grade follicular lymphoma at stage III and presented with lymphadenopathy and bulky mediastinal tumor causing cough and dyspnea. His laboratory data was normal except liver function tests that showed indirect hyperbilirubinemia (total bilirubin: 2.83, direct bilirubin: 0.32). HCV infection was detected in another patient with follicular lymphoma. This 62 years man presented at low grade and stage Is. His only presentation was huge splenomegaly and in lab data had leukopenia and anemia but LFT was normal.

The patients were followed during the 22 months for new sings, symptoms, laboratory findings and complications of NHL either before or after chemotherapy or radiotherapy sessions. During this time we found 12 cases that had relapse and 14 cases who died.

Results at the Time of Relapse

Twelve (10.9%) patients had relapse after 22 months of follow up that included 7 males and 5 females with mean age of 39.9 years. The significant result is that all of these patients had extranodal involvement at relapse. The extranodal site of involvement was mainly neurologic that occurred in 5 out of the 12 cases. Bone marrow involvement happened in four patients that one of them showed neurologic involvement too. Two cases came with renal failure and one of the patients presented with cardiac tamponade. The complications at relapse included lower extremity lymphedema, subcutaneous nodule and infection. Based on laboratory data, none of the patients had leukopenia at relapse but 4 cases presented with thrombocytopenia and 8 patients had anemia. High serum ESR level was seen in 4 cases and high LDH level was present in 4 cases at relapse too. Mortality after 22 months follow up was seen in fourteen patients (12.73%).

Discussion

Non-Hodgkin's lymphoma is a heterogeneous type of neoplasm with a vast variety of signs, symptoms, complications, morphologic and immunohistochemichal types which can involve almost any part of the body. During the last twenty years ago its prevalence has increased. The successful treatments and survival rate of the patients with this malignant tumor are also significant. Bearing in mind all the signs, symptoms and histopathologic findings, physicians would be able to diagnose the disease sooner when the rate of remission is higher.

Like many other studies we found that lymphoma is more common in male patients with an overall male to female ratio of 1.62 in this study. However we found that this ratio is reverse with a significant difference in patients who had high serum ESR level at presentation. This difference can be due to the etiologic factors in evolution of this malignant disease.

Another significant result in this study was the higher frequency of anemia in male cases compared to females. Although anemia is more common among women in general population, the high male to female ratio of anemia in this study can be due to the higher frequency of bone marrow involvement in males (male to female ratio: 2.33) and higher incidence of stage IV of NHL in male patients compared to female ones. Moullet et al. (1998) showed that anemia is an important adverse prognostic factor in NHL patients particularly if bone marrow is involved too. However, considering anemia in mortalities we didn't notice any significant difference in mortality rates between male and female cases in this study.

In age dispersal those patients who are diagnosed at low grade are mostly older than the patients at intermediate and high grade. Comparing to Western countries, we can see that although this age difference has decreased, Iranian patients who present with B-cell NHL at more advanced grades are still younger than West patients (Roman et al., 2011). Present study showed that intermediate grade is the most common grade in patients with NHL (57.8%), which can be due to the high frequency of DLBCL that is

mainly in the category of intermediate grade.

There is also a gender and age disparity between sub-types of lymphoma that may be indicative of different sub-type etiologies. Overall median age of B-cell NHL in Roman's study was 70 years while in our study results showed 50 years. As it is mentioned by Hashemi-Bahremani's et al (2007) too, the incidence of lymphoma is at younger ages in Iran compared to West.

Lymphoma sub-type frequencies showed that, the same as many other studies diffuse large B cell lymphoma is the most frequent sub-type of NHL, accounting for sixty percent of the patients. And in addition to small lymphocytic lymphoma and follicular lymphoma this rate increases to more than seventy percent. Based on Roman and Smith's study DLBCL, follicular lymphoma and marginal zone lymphoma are respectively the most common sub-types that account for more than seventy percent of total cases (Hingorjo et al., 2008, Roman et al., 2011). Another study that was done in Lebenan showed that DLBCL accounted for 50.6% and follicular lymphoma 23% of NHLs. They also showed that frequency of follicular lymphoma is higher compared to far eastern, European and American countries (Sader-Ghorra et al., 2014).

NHL is the main cause of lymphadenopathy between patients older than 50 years old (Albaseri et al., 2014). on the other hand lymphadenopathy is a common sign of NHL in many studies. Hingorjo et al. (2008) showed that lymphadenopathy is the most common sign in these patients and the most common site of lymphadenopathy was para-aortic area followed by cervical and axillary regions. However, in our study the most common presentation was extranodal signs and symptoms followed by lymphadenopathy and "B" symptoms respectively. Cervical region was the most common site of lymph node involvement.

Extranodal NHLs has increased more rapidly than the nodal form, especially in developing countries with an increase in diffuse pattern and more aggressive types (Bhattacharya et al., 2013). In this study near sixty percent of patients presented with extranodal signs and symptoms with gastrointestinal dominancy. Other studies has almost the same results: F. d'Amore et al. (1991) showed that out of 1257 newly diagnosed NHL patients, 37% had extranodal involvement and the GI tract was the most common site accounting for 30% of the patients. Extranodal lymphoma was more common in males than females and primary extranodal lymphoma was more common between female group of NHL than the male patients in this study. In the study more female cases showed thyroid and salivary glands lymphomas with a male to female ratio of 0.14 and 0.3 respectively while there wa s a male predominance for other sites of involvement (d'Amore et al., 1991)

At relapse, all the patients had extranodal involvement in which the most common type was neurologic followed by bone marrow involvement. The most common stage at relapse was stage IV. Based on the study of Biswamit Bhattacharya et al relapses were usually outside of the primary site. Fifty percent of relapses were seen in follicular lymphoma patients. Nodal relapses that were distal to the primary site were seen in six out of eight relapses and relapses more often happened in low grade patients that were treated compared to the high grade lymphomas with remission. That may show an indolent course for low grade lymphomas after remission (Bhattacharya et al., 2013).

All of the patients with bone marrow involvement in this study had some kind of hematologic abnormalities based on CBC data including mild to severe anemia, leukopenia and/or thrombocytopenia. The lower rate of bone marrow involvement (11%) comparing MG. One study that showed thirty two percent, means that molecular studies should be done on all the bone marrow samples disregarding for pathologic results, thus we might detect some cases with bone marrow involvement that were morphologically negative (Conlan et al., 1990).

Long term complications of NHL can be divided into secondary malignancies and late non-neoplastic complications. In this study we detected 3 cases of secondary malignancies including two cases with leukemia (CLL and CML) and one transitional cell carcinoma (TCC) of bladder. In a study done by Ng et al. (2011) the long term complications of lymphoma and its treatment were reviewed. It was showed that NHL survivors are at a greater risk for second malignancies such as myelodisplasia, acute myelogenous leukemia, and several solid tumors including cancers of bladder, lung, GI tract, head, neck, thyroid, CNS, sarcoma, melanoma, nonmelanomous skin cancers, and mesothelioma. Recent studies showed a significant risk of acute leukemia after NHL, with Relative risks ranging from 1.7 to 8.8 compared with general population. This increased risk is mostly related to alkylating chemotherapy agents like chlorambucil and cyclophosphamide. Long term non-neoplastic complications were more common in our study including post chemotherapy or radiotherapy complications that were renal failure, hypocellular marrow and pancytopenia, hypothyroidism (each in one case) and infective complications with fever in three of the cases. Late non-neoplastic complications were seen in 46% of 757 patients who were followed for 9.4 years after NHL treatment. The most common complications were cardiac disease and infertility. Other complications were disabling neuropathy, renal insufficiency, GI toxicity, and lung fibrosis.(Hingorjo et al., 2008) Febrile neutropenia as a common and serious complication of chemotherapy treatment was studied in patients with NHL (Schwenkglenks et al., 2013).

There was an increasing incidence of NHL in most developed countries during 1990s that may be due in part to improvement of diagnostic procedures and the epidemic of AIDS while the decline in incidence rate after 1990 is simultaneous with success of anti-retroviral therapies and decrease in AIDS incidence (Jemal et al., 2011). The increasing incidence rate of 3-4% per year since 1970-1980 and 1-2% annually by 2005 has been noticed worldwide especially in patients older than 55 years (Jemal et al., 2011, Müller et al., 2005). Therefore it is essential to have more researches regarding other factors that affect patients in development of NHL. Molecular studies especially to find bone marrow and neurologic

involvements may be useful for an accurate diagnosis and finding etiologic factors of NHL so that we can understand better this malignant heterogeneous disease that presents with many different signs and symptoms and its prevalence is still increasing although it can be treated successfully if diagnosed soon.

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