



Clinical Spectrum of non-Hodgkin Lymphoma: A Hospital Based Study of 410 Cases.

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Keywords: Clinical Manifestation, "B" Symptoms, Lymph Node, Hepatomegaly, Splenomegaly, Non-Hodgkin Lymphoma.

ABSTRACT

Background: Lymphoma can be misdiagnosed due to lack of awareness of various clinical features. There is a rising incidence of lymphomas over the past few years. Several non Hodgkin lymphoma can present with different 'B' symptoms, different clinical signs and different sites of involvement. This study was done to evaluate the different clinical features and lymph node involvement at presentation in non Hodgkin lymphoma.

Methods: 410 diagnosed and treated cases of non-Hodgkin lymphoma were selected from Kasturba Medical College, Manipal between Jan 2009 and December 2012. Clinical history, 'B' symptoms, laboratory investigations, including imaging procedures were noted in all the cases. The diagnosis of lymphoma was based on histology, IHC and WHO-2008 classification.

Results: Out of 410 cases of non Hodgkin lymphoma, Nodal lymphomas comprised of 57.34% of total cases while extranodal lymphomas accounted for 42.6% of cases. B cell lymphoma accounted for 80.3% and T cell lymphoma were 19.6%. Most of the patients with NHL were in the age group of 50-60 yrs. 69% of cases were males while 31% of cases were females. Anemia was the commonest presenting feature among 'B' symptoms and cervical lymph node was most commonly involved lymph node.

Conclusion: The clinical spectrum of lymphoma sometimes delays its diagnosis, leading to its eventual presentation in late stages. Awareness is required among the health professionals regarding its varied clinical presentations to diagnose at the earliest.

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Introduction

There is a rise in incidence of lymphomas over the past few years. Non-Hodgkin lymphomas (NHL) can arise in lymph nodes, other lymphatic tissues and extranodal organs.¹ Lymphoma can occur at any age; however, it has a bimodal presentation with one peak in 0-10 years of life and another peak after 50 years. Patients with lymphoma, both Hodgkin and Non-Hodgkin usually present with “B” symptoms or with enlarged lymph nodes. “B” symptoms refer to systemic symptoms of fever, night sweats and weight loss. 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, central nervous system, liver, or bone, thus leading to atypical presentations.² Due to the varied clinical manifestations, many patients are misdiagnosed and mistreated.³ Patients having “B” symptoms show a more severe condition than asymptomatic patients with the same cancer stage, tumour location or size. Onset of “B” symptoms at the time of diagnosis suggests that lymphoma is progressing.⁴ This study was planned to evaluate the varied clinical presentations of non Hodgkins lymphomas and the patterns of lymph node distribution.

Materials and Methods

Diagnosed and treated 410 cases of non Hodgkin lymphoma were selected from the Department of Pathology, KMC, Manipal between Jan 2009 and December 2012 (4 years), between the age group of 1–90 years. Clinical history, physical examination and basic laboratory investigations, including imaging procedures and bone marrow examination were done in all the patients. The diagnosis of lymphoma was based on histology, IHC and WHO-2008 classification. Appropriate clinical information regarding age, gender, anatomic location and occurrence of “B” symptoms were noted which included fever (temperature $>38^{\circ}\text{C}$ [$>100.4^{\circ}\text{F}$] for 1-2 weeks), weight loss of $>10\%$ of body weight in ≤ 6 months and drenching night sweats. Types of NHL, anatomic location and occurrence of “B” symptoms were confirmed with the help of medical records. Data was statistical analysed using SPSS - soft ware.

Result

Out of 410 cases, nodal lymphomas comprised of 57.34% of cases while extranodal lymphomas accounted for 42.6% of cases. B cell lymphoma accounted for 80.3% and T cell lymphoma were 19.6%. Most of the patients with NHL were in the age group of 50-60 yrs. There was male preponderance with 69% of cases being males while 31% of cases were females.

In the present study anemia was the commonest presenting sign and accounted for 90.4% of the cases followed by

other ‘B’ symptoms like weight loss and fever which was observed in 23.9% and 21.7% of cases respectively. Hepatomegaly and splenomegaly was observed in 23.1% and 20.9% of cases respectively, while effusion was noted in 10.9% of cases. (Table 1)

55.8% of NHL cases presented with cervical lymphadenopathy, followed by supraclavicular lymph node enlargement, which was involved in 39.5% of NHL cases and axillary lymph node involvement was seen in 32.4%. of case Mesenteric, inguinal and mediastinal lymph node involvement was seen in 28.4%, 25.6% and 12.6% of NHL cases respectively. (Table 2)

Discussion

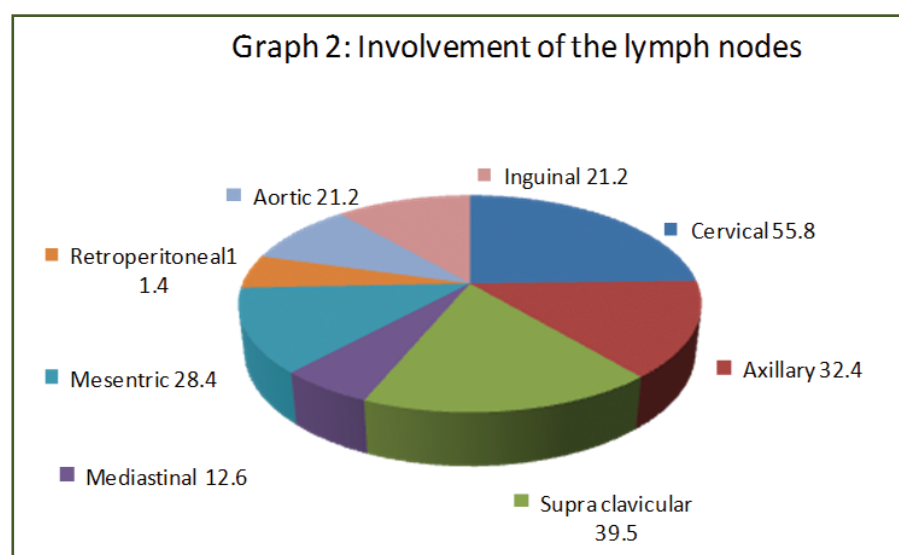
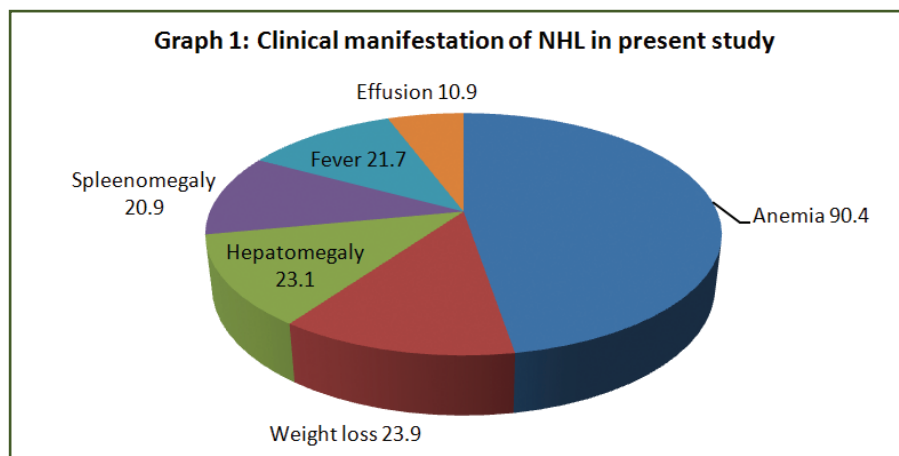
The incidence of the subtypes of non-Hodgkin lymphoma shows geographical variations, differs in history and clinical presentation. These variations are dependent upon environmental influences, such as local common viral infections including Epstein Barr virus and socioeconomic factors.⁵

Hingorjo et al⁵ and Hassan et al⁶ have documented anemia in 100% and 87.5% of NHL cases respectively, which is similar to our present study. However Cunlan et al⁷, Ghosh et al⁸ and Idris et al⁹ have documented much lesser incidence of anemia with 55%, 49% and 65% of NHL cases respectively. (Table 1)

Multiple mechanisms contribute to the development of anaemia in NHL patients. These include anaemia of chronic disease (ACD), autoimmune haemolytic anaemia (AIHA), bone marrow infiltration, nutritional deficiencies and blood loss. Cytokines such as IL-6 have been shown to increase hepcidin levels which result in iron restriction and signs of anaemia of chronic disease.¹⁰ It is now recognized that anaemia may lead to symptoms that adversely affect physical status and diminish functional capacity and quality of life.¹¹⁻¹² The presence of anaemia is also associated with poorer prognosis and increased mortality.¹³⁻¹⁴ Anemia in the presence of bone marrow involvement has poor prognosis.⁵ However, anemia is poorly recognized and under-treated.

Hepatomegaly was observed in 83.6% and 45% of cases by Hingorjo et al⁵ and Hassan K et al⁶ respectively, which is much higher in comparison with our study. However, Idris et al⁹ has documented 22% of cases which is similar to our present study. (Table 1)

Lymphoma cell infiltration of the liver with hepatomegaly is more common in NHL than in Hodgkin Lymphoma (HL), with 16%–43% of cases showing hepatic involvement.¹⁵⁻¹⁶ Extrahepatic obstruction is also more common in NHL than in HL, and hepatic infiltration is more common in low-grade B-cell lymphomas than in high-grade lymphomas. Acute



hepatic failure can occur in NHL as seen in HL, which is caused by sudden ischemia related to massive infiltration of the sinusoids or replacement of liver parenchyma by malignant cells.¹⁷ Elevated level of serum LDH is also often seen in patients with NHL, especially in highly aggressive type such as Burkitt or lymphoblastic lymphoma, reflecting high tumor burden, extensive infiltration of the liver, and coincident immune-mediated Hemolytic Anemia, which are associated with poor prognosis.¹⁵

Splenomegaly was observed in 44.8% and 47.5% of cases by Hingorjo et al⁵ and Hassan K et al⁶ respectively, which is much higher in comparison to study by Idris et al with 22% of cases and to our present study.(Table 1)

Splenomegaly is an uncommon presenting feature of non-Hodgkin lymphoma. B-cell types of NHL involving spleen are predominantly low grade and occur in older individuals whereas the T-cell NHL are predominantly high grade and occur in adolescents and young adults.¹⁸

Fever was observed in 67.3%, 62.5% and 72% of cases by Hingorjo et al⁵, Hassan K et al⁶ and Idris et al⁹ respectively. These associations were much higher compared with our study (Table 1). However Sra N et al¹⁹ observed 22% of cases presenting with fever which is similar to our study.

In most patients, no particular fever pattern emerges that is pathognomic of cancer. Fever can occur during the day or night, although drenching night sweats are often a manifestation of malignancy and, if persistent, should prompt the clinician to consider neoplastic disease. Cytokines (endogenous pyrogens) induce prostaglandin E₂, which in turn causes hypothalamic set point surge, and fever. Interleukin-1 (IL-1), TNF (Tumour Necrotic Factor), Interleukin-2 (IL-2), Interleukin-6 (IL-6), Interleukin-12 (IL-12), or interferons are elevated with neoplasm or infection²⁰. While the cause of elevated cytokines during infection is precipitated by pathogens, the trigger in cancer is unclear. One study found that activation of IL-1? was

induced by mutated RAS²¹. Another possibility includes inflammation secondary to ulceration or necrosis caused by the tumor itself. A key player in this cytokine jumble is IL-6. High levels of IL-6 are seen in Hodgkin Lymphoma, Diffuse Large Cell Lymphoma, and CLL. IL-6 is associated with B-symptoms and has prognostic value in these three cancer types.²²⁻²⁶. In Diffuse-Large Cell Lymphoma, the independent factor that most correlates with complete remission and disease free survival is IL-6 serum level²⁷.

Weight loss as presenting symptom was observed with almost similar incidence by most of the study groups. (Table 1) An 'unexplained' weight loss means a weight loss of more than a tenth of your total body weight over a period of <6 months. The pathologic mechanism underlying weight loss and cachexia are poorly understood. Soluble factors such as tumor necrosis factor- alpha (TNF- α), interleukin-1 (IL-1), interferon γ (IFN- γ) and interleukin-2 (IL-2) are involved in the development of tumor cachexia²⁸. Weight loss can also occurs because aggressive lymphoma cells place an heavy demand on body and use up its resources to feed the cancerous cells.²⁹

The lymph node involvement of NHL and HD are distinctive, with HD presenting with regional enlargement of single group of peripheral lymph nodes as opposed to disseminated nodal involvement in NHL.

Lymphadenopathy is a common sign of both benign and malignant diseases.³⁰ Krol et al¹, Naz et al⁴, Hassan et al⁶ and Hahn et al³¹ have also documented cervical lymphadenopathy to be the most common presenting symptom. (Table 2) Supraclavicular lymph node was the second most common lymph node involved in our study, However Hahn et al³¹ reported aortic lymph node as second most common lymph node, Naz et al⁴ and Krol et al¹ documented inguinal lymph node as second most common lymph node. Krol et al¹ in their study showed mediastinal lymphadenopathy in 11.4%, similar to our study. (Table 2)

Presence of lymphoid cells in Fine Needle Aspiration Cytology of lymph node are usually considered to be associated with the diagnosis of lymphoma; however, there are other Benign conditions involving lymph nodes like tuberculosis, some metastatic tumours with lymphocytes, that may be misleading.³² Hence these patients with NHL may be misdiagnosed and treated incorrectly with antituberculous 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 NHL.⁵ Clinicopathologic features and lymph node involvement by NHL as observed in our study and other asian studies show variation from NHL encountered in the Western world.^{4,5} Hence the knowledge of these variations is at most necessary.

Table 1: Clinical manifestation of NHL at presentation in various studies compared with present study.

Symptoms	Present study	Hingorjo et al ⁴	Cunlan et al ⁵	Hahn et al ⁶	Hassan K et al ⁷	Ghosh J et al ⁸	Idris et al ⁹	Sra N et al ¹⁰
Fever	21.7	67.3	-	16.7	62.5	-	72	22.0
Weight loss	23.9	24.8	-	26.4	7.5	-	47	25.0
Anaemia	90.4	100	55	-	87.5	49%	65	-
Hepatomegaly	23.1	83.6	-	-	45.0	-	22	-
Splenomegaly	20.9	44.8	-	-	47.5	-	18	-
Effusion	10.9	28.5	-	-	-	-	-	-

Table 2: Frequency of lymph node involvement in NHL in various studies compared with present study.

Lymph nodes	Present study	Krol et al ¹	Hahn et al ⁶	Hassan K et al ⁷	Naz et al ⁴	Sra N et al ¹⁰
Cervical	55.8	40.7	52	40	32.3	62.5
Axillary	32.4	21.8	13.1	10	9.6	-
Supra clavicular	39.5	-	-	20	3.2	-
Mediastinal	12.6	11.4	12.8	5	-	-
Mesenteric	28.4	-	13.7	10	-	-
Retroperitoneal	11.4	-	-	2.5	-	-
Aortic	21.2	-	20.1	-	-	-
Inguinal	25.6	26.1	15.8	-	14.5	14.5
Waldeyers ring	12.1	-	-	-	-	12.5

Conclusion

Incidence of NHL is on the rise specially extra-nodal NHL with wide variations in the presentation of the disease due to involvement of different sites. The presence or absence of “B” symptoms has prognostic significance and is reflected in the staging of NHL. NHL presents commonly as Cervical lymphadenopathy, Anemia, weight loss and hepatomegaly with a close resemblance to tuberculosis and other disorders. This may cause difficulty to practitioners for early diagnosis. An awareness regarding the clinical manifestations and sites of involvement of NHL may help in early diagnosis and treatment.

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