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Correlation between clinical features and immunohistochemistry profile of lymphoma patients

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Abstract

Context: Lymphomas are malignant neoplasm of lymphoid cell lines commonly involving lymph nodes and account for up to 3% of all malignancies. These are mainly classified as either Hodgkin's or Non-Hodgkin's Lymphoma (NHL). Immuno-Histochemistry (IHC) is an integral part of diagnostic Hematopathology. Since no study has been done on this subject in our institute; hence, we conducted this study.

Aims: To study the correlations between Immuno-Histochemistry and clinical profile of lymphoma patients.

Methods and Material: The present cross sectional study was carried out in 32 Biopsy and IHC proven newly diagnosed patients of lymphoma in the Dept. of Clinical Hematology of Pt. B.D. Sharma PGIMS, Rohtak from October2014-February2016.

Results: Mean age of the study population was 49.29±15.99 with a range of 18-75 years. In our study, majority of patients were male i.e. 19 (59.37%) and 13 (40.62%) were female. It shows male to female ratio 3:2. Lymph node swelling was most common symptom present in a total of 26 (81.25%) cases. Out of Various CD markers noted in all the patients, CD 20 was the most common marker seen in 26 (81.25%) cases. On final Histopathological and IHC examination, Non-Hodgkin's Lymphoma was diagnosed in 28(87.5%) cases and Hodgkin's Lymphoma in 4 (12.5%) cases and the most common sub type of NHL was DLBCL seen in 18 patients. On Immuno-histochemistry of patients, who found for CD 10 positive; presented in advanced stage and nodal presentation, whereas CD 10 negative patients presented in early stage (Grade I and II) and Extranodal presentation.

Keywords: Lymphomas, Immuno-Histochemistry (IHC), Hodgkin's, Non-Hodgkin's Lymphoma

Introduction

The Lymphomas are malignant neoplasm of the lymphoid cell lines commonly involving lymph nodes, spleen, bone marrow and less commonly pharyngeal tissues, salivary glands, thymus, the GIT, CNS, skin etc. and account for up to 3% of all malignancies. These are mainly classified as either Hodgkin's or non-Hodgkin's lymphoma (NHL) and NHL is further sub

typed either B/T-cell NHL. The DLBCL appears to be the most common type of primary B- NH.[1.2]

Immuno-Histochemistry (IHC) is an integral part of diagnostic Hematopathology. Although in the early 1980s a routine panel included less than 10 antibodies, the current diagnostic armamentarium includes more than 50 antibodies and more than 300 current cluster designation (CD) antigens list[3].Since no antigen is totally specific; therefore, immunostaining must be interpreted in the context of a panel so as to avoid errors in assignment of cell lineage or of an abnormal phenotype.

Since the advent of the immunological characterization of malignant lymphomas, most Non-Hodgkin's lymphomas of B and of T cell origin have been clearly defined, and the correlation between their immunological characteristics and morphological appearances are well established.

To the best of our knowledge, very few studies were available and no study has been done on this subject in our institute; hence, we conducted this study.

Aims and Objectives

To Study The Correlations between Immuno-Histochemistry and Clinical Profile of Lymphoma Patients.

Subjects and Methods

The present study was carried out in 32 Biopsy and IHC proven newly diagnosed patients of lymphoma in the Dept. of Clinical Hematology of Pt. B.D. Sharma PGIMS, Rohtak , after taking informed consent and applying the inclusion/exclusion criteria given below from October2014-February2016.

Inclusion Criteria

1) Patient 18 years of age and above.
2) Newly diagnosed Biopsy and IHC proved cases of lymphoma.

Exclusion Criteria

1) Already treated patients for lymphoma.

Method of Study

Patient who fulfilled above mentioned inclusion criteria were selected as case in the present study. Detailed history of patients were taken for fever, night sweats, weight loss, itching ,any swelling or palpable lumps, anorexia, symptoms of pallor, bleed, weakness, fatigue.

Physical examination was done on every patient for fever, lymphadenopathy, splenomegaly, hepatomegaly, jaundice and bony tenderness etc. and following investigations including complete blood count with peripheral blood smears, liver function test (SGOT, SGPT, serum bilirubin), renal function test (blood urea, serum creatinine), Chest X Ray, Ultrasonography whole abdomen, serology for HIV I and II, HCV,HBsAg, Bone marrow biopsy and CT chest and abdomen were done in all patients.

Lymph node biopsy was subjected to Histo-Pathology and Immune-Histochemistry panel marker which was decided according to the morphology of malignant cell population and commonly following markers were applied.

i) T cell markers CD3, CD4, CD5, CD7

ii) B cell markers CD19, CD20, CD22

iii) Hodgkin lymphoma CD 15, CD30, CD45

Results

The present study was carried out on 32 newly diagnosed patients of Lymphoma. Patients were followed up in the department of clinical haematology clinic of Pt. B.D. Sharma PGIMS, Rohtak. The following results were noted:

Table 1: Demographic profile (n=32)

Age (yrs) (Mean±SD) (Range)	49.29 ± 15.99 18-75
Sex Male Female	 19 13
Lymph Node Swelling (LAP)	26
B-Symptoms	
Fever	17
Weight loss	15
Fatigue	14
Loss of appetite	9
Night sweats	5
Respiratory distress	1
Itching	1

Table 1 shows age distribution and clinical features lymphoma patients. In the present study, maximum numbers of patients were in the 5th to 6th decade of their life. A total of 9 (28.12%) patients with age range of 51-60 years followed by 8(25%) with >60 years found. Mean age of the study population was 49.29±15.99 with a range of 18-75 years. In our study, majority of patients were male i.e. 19 (59.37%) and 13 (40.62%) were female. It shows male to female ratio 3:2. Lymph node swelling was most common symptom present in a total of 26 (81.25%) cases, followed by fever 17(53.12%), weight loss (46.87%) and loss of appetite in 9(28.12%) cases. Respiratory distress and itching was found only in 1 (3.12%) case.

Table 2: CD markers (n=32)

CD markers	No. of patients	Percentage
CD 20	26	81.25
CD 5	16	50
CD 10	12	37.5
CD 30	7	21.87
BCl-2	7	21.87
BCl-6	4	12.5
CD 3	3	9.37
ALK	3	9.37
CD 15	2	6.25
CD 23	2	6.25
CD 45	2	6.25
Others	6	18.75

Out of Various CD markers noted in all the patients, CD 20 was the most common marker seen in 26 (81.25%) cases followed by CD5 in 16 (50%) cases, CD10 in 12 (37.5%), CD30 and BCl-2 in 7 (21.8%), CD7 (21.87%), and CD15 in 2 (6.25%) cases.

Table: 3 Final diagnosis (n=32)

Lymphoma	No. of patients	Percentage
Non-Hodgkin's lymphoma	28	87.5
Hodgkin's lymphoma	4	12.5
Total	32	100%

On final Histopathological and IHC examination, Non-Hodgkin's Lymphoma was diagnosed in 28(87.5%) cases and Hodgkin's Lymphoma in 4 (12.5%) cases.

Table 4: Distribution of Non-Hodgkin's lymphoma (n=28)

Non-Hodgkin's lymphoma	No. of patients	Percentage
B-Cell (n=25)	18	66.66

Non-Hodgkin's Lymphoma (DLBCL)		
Non-Hodgkin's Lymphoma (FOLLICULAR LYMPHOMA)	3	11.11
Non-Hodgkin's Lymphoma (MANTLE CELL LYMPHOMA)	2	7.40
Non-Hodgkin's Lymphoma STAGE III EXTRA NODAL MARGINAL ZONE B CELL LYMPHOMA (MALT TYPE)	1	3.70
Non-Hodgkin's Lymphoma (SMALL LYMPHOCYTIC TYPE)	1	3.70
T-cell type (n=3)		
Non-Hodgkin's Lymphoma (ANAPLASTIC LARGE CELL LYMPHOMA)	2	7.40
Non-Hodgkin's Lymphoma (PERIPHERAL T CELL TYPE)	1	3.12

Table 4 shows distribution of Non-Hodgkin's Lymphoma in various subtypes. In the present study the most common sub type is DLBCL seen in 18 patients (66.66%) followed by mantle cell lymphoma in 2 (7.40%), Follicular lymphoma in 3 (11.11%), Stage III Extra nodal marginal zone B Cell Lymphoma in 1 (3.70%), Small Lymphocytic Type in 1 (3.70%), and Anaplastic Large cell Lymphoma in 2 (7.40%)patients.

Table 5: Primary / Secondary Extra nodal NHL (n=28)

NHL (n=28)	No. of patients	Percentage
Total Extra nodal	7	25%
Primary extra nodal	2	7.14
Secondary extra nodal	5	17.85

Table 5 shows distribution of Non-Hodgkin's lymphoma according to primary and secondary extra nodal. In the present study, we found 2(7.14%) cases with primary extra nodal and 5(17.85%) were secondary extra nodal.

Table 6: Staging (n=32)

Stage	No. of patients	Percentage
I	5	15.62
II	3	9.37
III	8	25
IV	16	50

All the patients were categorized according to their lymph node staging. In our study, a total of 16 (50%) cases categorized to stage IV, followed by 8(25%) cases each with category III. Only 3 (9.37%) patients of category II and 5 (15.62%) with category I found.

Table 7: Correlation between stage and Immuno-Histochemistry of DLBCL patients (n=18)

Parameters	No. of patients	Stage of disease n (%)
CD 10 +ve (Positive)	10 (55.55%)	Stage I – 1 (10%) Stage II – 1 (10%) Stage III – 2 (20%) Stage IV – 6 (60%)
CD 10 –ve (Negative)	8 (44.44%)	Stage I – 3 (37.5%) Stage II – 2 (25%) Stage III – 1 (12.5%) Stage IV – 2 (25%)

Table 7 shows correlation between stage and Immuno-Histochemistry of DLBCL patients. In our study, CD 10 positive cases found were 10 (55.55%) out of which 1 each of stage I and II, 2 with stage III and 6 with stage IV. Similarly, CD 10 negative cases were 8 (44.44%) out of which 3 with stage I, 2 each of stage II and IV and stage III had 1 case. This suggests that CD10 +ve patient presented in advanced stage of disease i.e. Grade III and IV (80%) whereas CD 10 –ve patient presented in early stage (62.5%) of disease.

Table 8: Correlation between clinical feature and Immuno-Histochemistry of DLBCL patients (n=18)

Parameters	Nodal n(%)	Extra nodal (primary / secondary)
CD 10 + ve (n=10)	9 (90%)	1 (10%) Secondary
CD 10 – ve (n=8)	2 (25%)	2 (25%) secondary 4 (50%) primary

Table 8 demonstrates correlation between clinical feature and Immuno-Histochemistry of DLBCL patients. In the present study, majority of CD 10 positive cases were having nodal presentation (90%) where as majority of CD 10 negative cases were having primary (50%) or secondary (25%) extra nodal presentation. It suggests that CD 10 +ve (positive) patients mostly present with nodal involvement whereas CD 10 –ve (negative) patients mostly present with extranodal presentation

Discussion

Lymphomas are heterogeneous group of Lympho-Proliferative malignancies which results from Clonal expansion of tumor cells derived from B, T, or NK cells. 85%-90% are derived from B cells. The two main types are Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma makes up about 90% of cases and includes a large number of subtypes.[1] These make up 3-4% of all cancers, making them as a group the seventh-most common form.[2]

1. Age distribution

In the present study, maximum number of patients was in the 5th to 6th decade of their life. A total of 9 (28.12%) patients with age range of 51-60 years followed by 8(25%) with >60 years found. Mean age of the study population was 49.29±15.99 with a range of 18-75 years. These findings were consistent with studies conducted previously by Hongorjo et al in 2008 and they found the median age between 52-62 years which is closely resembles to our study.[4] Similarly, Nair et al in 2016 conducted a national survey and found the median age of 54 years.[5] The median age of patient with NHL in India is lower by almost one decade compared to that of western population.[6]

2. Sex distribution

In our study, majority of patients were male i.e. 19(59.37%) and a total of 13 (40.62%) were female. It shows male to female ratio is 3:2 which closely resemble to previous studies. Aggarwal from India in 2013 conducted study and found the ratio of 2:1.[7] Likewise Nair et al in 2016 conducted a study and found the result 3.2:2 for the same.[5]

3. Systemic symptoms

We found Lymph node swelling as the most common symptom of our patients. Lymph node Swelling was present in a total of 26 (81.25%) cases, followed by fever 17(53.12%), weight loss (46.87%) and loss of appetite in 9(28.12%) cases. Respiratory distress and itching was found only in 1 (3.12%) case each. These results are consistently resemble of previous studies like Colombo et al in 2003 found most common clinical presentation of lymphoma were lymph node swelling (68%).[8]A similar study by Prakash et al in 2012 in

India found the most common symptom was Lymphadenopathy, in 66% of cases.[6]

In our study B-symptoms were present in 53 % of cases which is quiet similar to previous study done by Colombo et al in which B-symptoms were presented in 50% of cases.[8] The higher frequency of B-symptoms in India (40-60%) compared to developed nation (20-30%) may be due to the late presentation of patient for clinician and unawareness of the disease.

4. CD markers

Out of Various CD markers noted in all the patients, CD 20 was the most common marker seen in 26 (81.25%) cases followed by CD5 in 16 (50%) cases, CD10 in 12 (37.5%), CD30 and BCl-2 in 7 (21.8%), CD7 (21.87%), and CD15 in 2 (6.25%) cases. These findings correlated with many previous studies.

On final Histo-pathological examination, we observed Non-Hodgkin's Lymhoma in 28 (87.5%) cases and Hodgkin's Lymphoma in 4 (12.5%) cases. These results are consistently comparable with previous studies like Aggarwal et al in 2012 got results of 83.17% and 16.83 for non Hodgkin and Hodgkin lymphoma respectvly.[7]

In the present study the most common sub type was DLBCL seen in 18 (66.66%) followed by mantle cell lymphoma in 2 (7.40%), Follicular lymphoma in 3 (11.11%), Stage III Extra Nodal Marginal Zone B Cell Lymphoma in 1 (3.70%), Small Lymphocytic Type in 1 (3.70%) and Anaplastic Large cell Lymphoma in 2 patients(7.40%). These results resemble to previous study done by Prakash et al in 2012 with results of 71% of DLBCL.[6] Another study done by Aggarwal et al (A multicentre registry based study from India) showed the results of 55% of DLBCL followed by Follicular then mantle cell Lymphoma.[7] Likewise a study done by Naresh et al in 2000 showed the results DLBCL (34%), Follicular (12.6%), B cell small Lymphocytic Lymphoma (5.7%), Mantle cell lymphoma (3.4%), marginal zone b-cell lymphoma including malt (8.2%). Follicular and mantle cell lymphoma are less common in India compared to Europe and the USA.

Distribution of Non-Hodgkin's lymphoma cases were divided into B-cell and T-cell types. In the present study, a total of 25 cases (96.42%) with B cell Non-Hodgkin's lymphoma and 3 cases (3.57%) with T-cell NHL sub type was found. The results of study can be correlated with Nair et al in 2016 which showed T-cell lymphoma present with >10% of total cases.[5] The frequency of T-cell lymphoma is quiet lower than in western countries.[6]

Non-Hodgkin's Lymphoma divided into primary and secondary extranodal category. In the present study, we found 2 (7.14%) cases with primary extranodal and 5 cases (17.85%) were secondary extranodal. The results are quiet similar of various studies and literature in which extranodal involvement of Non Hodgkin's lymphoma are 25-40%. Hassan et al conducted a study in 1995 and showed the results of Extranodal lymphoma were 15% of total cases.[10]

All the patients were categorized according to their lymph node staging. In our study, a total of 16 (50%) cases categorized to stage IV, followed by 8(25%) cases each with category III. Only 3 (9.37%) patients of category II and 5 (15.62%) with category I found.

The results are quiet comparable with previous studies, Aggarwal et al found the results that high grade lymphoma (Grade IV) was the most common subtype 44.2%, followed by intermediate (39%) and low grade Lymphoma (12.2%).[7] Similarly, Prakash et al showed the results that most common subtype was advanced stage (Grade IV) 47%.[6]

Correlation between clinical feature and Immunohistochemistry of Lymphoma patients

Depending upon their progression and clinical presentation; lymphomas are divided into indolent (e.g. small lymphocytic lymphoma) and aggressive (e.g. Burkitt lymphoma, diffuse large B-cell lymphoma and Mantle cell lymphoma). Each category has their clinical presentation and IHC (Immuno-Histochemistry) finding. However, in some patients, expression of aberrant CD marker or loss of some CD marker has some impact on clinical presentation.

Table 7 shows correlation between clinical feature and immunohistochemistry of DLBCL patients. In our study, CD 10 positive cases found were 10 (55.55%) out of which 1 each of stage I and II, 2 with stage III and 6 with stage IV. Similarly, CD 10 negative cases were 8 (44.44%) out of which 3 with stage I, 2 each of stage II and IV and stage III had 1 case. It suggests that CD-10 +ve DLBCL patients mostly presented in late stage (Grade III & Grade IV 80%) whereas CD-ve DLBCL patients frequently had a localised disease (Stage I & II 62.5%) and etc.

Table 8 demonstrate correlation between clinical feature and Immunohistochemistry of DLBCL patients. In the present study, CD 10 positive nodal cases were 9 (50%) and 1 with extra nodal (primary/secondary). Also CD 10 negative nodal and secondary extra nodal cases were 2, while 4 cases (50%) were of primary extra nodal. It suggests that CD-10 -ve DLBCL patients more often exhibited Primary extranodal origin (50%) than CD-10 +ve patients (10%). These results resemble with previous study done by Colomo et al[40] (2003) in which they found CD10 –ve DLBCL patients exhibited primary extranodal origin in 59% patients, CD10+ve DLBCL presented in advanced stage (73%) in contrast to CD10 –ve DLBCL in 30% of patients.

A study done by Colomo et al between September 1987 and September 1998 to analyse the relationship between Immuno-histochemistry (IHC) profile and main clinical feature and outcome in diffuse large B-cell lymphoma (DLBCL) in 128 patients consecutively diagnosed with DLBCL in institution. Cells from each patient were Immunostained with CD20, CD79a, CD5, CD10, bcl-6, MUM1, CD138, bcl-2, p53, p27. Patients with CD10−lymphomas more frequently had a localized Ann Arbor stage (I or II), normal serum LDH levels, and low- or low/intermediate risk. On the other hand, CD10+patients presented in an advanced stage (III or IV).[8]

Stein et al studied between 1985 and 1998 to analyse $CD30^+$ Anaplastic Large cell Lymphoma & its clinical features and found that Anaplastic Lymphoma Kinase positive $(ALK)^+$ Anaplastic Large Cell Lymphoma (ALCL) predominantly affects young male patients and, if treated with chemotherapy, has a favourable prognosis. Whereas ALK- ALCL occurs in older patients, affecting both genders equally and having an unfavourable prognosis.[11]

Another study done by Poeta et al between 1989 to 1999 to analyse Clinical significance of CD38 expression in Chronic Lymphocytic Leukemia and found that In B-cell Chronic Lymphocytic Leukemia (B-CLL) CD38 positivity associate with aggressive behaviour of disease, higher tumour burden (Lymphadenopathy / Splenomegaly) and a lymphocyte doubling time less than 12 months.[9]

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