Clinicopathological and Immunophenotype Spectrum of Malignant Lymphoma in Eastern India Population – A Tertiary Care Hospital Study

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ABSTRACT

BACKGROUND

Malignant lymphoma (ML) is one of the most common cancers, accounting for 3.37 % of all malignancies and is more prevalent in developed countries. Distribution of different subtypes of ML varies in different geographical locations according to the World Health Organization (WHO) classification.

METHODS

This is a retrospective study conducted over a period of one and a half years (July 2017 - December 2018) among hundred and six cases of ML, which were archived from the database of a tertiary care teaching hospital, Bhubaneswar. Clinical history, radiological findings, biochemical and haematological profile were taken into account. Haematoxylin and eosin stained slides and immunohistochemical (IHC) slides were studied by three pathologists including the first author. The diagnosis was reviewed after doing a battery of immunohistochemical lymphoma markers and categorized as per World Health Organization (WHO) 2016 classification. One year follow up was done after administration of chemotherapy.

RESULTS

Incidence of Hodgkin Lymphoma (HL) is much lower than Non-Hodgkin Lymphoma (NHL), with a HL to NHL ratio of 1 : 2.78. Amongst HL, mixed cellularity (MC) was the commonest type (57.14 % of HL) and in NHL, diffuse large B cell lymphoma (DLBCL) was the commonest subtype (53.85 % of NHL). The commonest nodal site involved irrespective of type of B cell NHL was cervical lymph node and that of extranodal site was stomach. T cell NHL showed peripheral T cell lymphoma (PTCL) as predominant subtype (10.26 % of NHL) majority of which showed extranodal involvement.

CONCLUSIONS

Recent WHO classification (2016) has made significant alterations to the previous (2008) classification. This is based on immunohistochemical profile, molecular and cytogenetic studies. This study attempts to categorise various lymphomas as per WHO (2016) classification which not only has diagnostic implication but also has significant prognostic and predictive value.

KEYWORDS

Malignant Lymphoma, Eastern India, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Diffuse Large B Cell Lymphoma, Peripheral T Cell Lymphoma

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BACKGROUND

Lymphoid neoplasms are a group of distinct entities with widely varying clinical features, histology, immunophenotypes and genetic abnormalities. The World Health Organisation (WHO) classification of lymphoid neoplasm encompasses not only Hodgkin's (HL) and Non - Hodgkin's lymphoma (NHL), but also plasma cell neoplasm and lymphoid Leukemia representing solid and circulating phases of the same diseases.[1,2,3] Malignant lymphoma (ML) comprises of 3.37 % of all malignancy world wide.[4] The incidence of malignant lymphoma has a marked geographic variations, much higher in North America, Australia, New Zealand and Europe and lower throughout Asia and Africa except at endemic areas of Burkitt lymphoma (BL).[4,5,6] The variation suggests the influence of ethnicity, environmental influence, higher socio - economic status including dietary habits, sedentary lifestyle, increased life span and exposure to carcinogens.[7] The incidence is strongly dependant on the infectious aetiology, for example Human immunodeficiency virus (HIV) / Acquired immunodeficiency syndrome (AIDS) epidemic leads to increased Non-Hodgkin's lymphoma (NHL) in The United States.[8,9,10] Increased Epstein - Bar virus (EBV) infection in Africa leads to BL and due to increase in Helicobacter pylori (H. Pylori) infection in Japan there is prevalence of extranodal marginal zone B cell lymphoma (MALToma).[11,12,13,14] The trend of HL is consistently lower than NHL and has a decreasing trend.[15] But it has an increased trend in females particularly in developed countries due to decreased parity, elderly primigravida, childhood infections etc.[16,17] Majority of the NHL occurs at higher age (sixth - seventh decade), whereas Acute lymphoblastic leukemia / lymphoma (ALL), BL, MALTomas occur in younger age.[18] The vice versa is true for HL, which is predominant in childhood and young age followed by a second peak in older age. Western population shows increased incidence of Chronic lymphocytic lymphoma / small lymphocytic lymphoma (CLL / SLL) and Follicular Lymphoma (FL) whereas the eastern population (Asian countries) has predominance of Diffuse large B cell lymphoma (DLBCL), MALToma, Natural killer / T cell lymphoma (NK / T cell lymphoma).[1,3,14,18,19,20] The aim of the study is to find out the incidence of various lymphomas based on clinico - histological parameters and to categorise various lymphomas (HL AND NHL) based on immunohistochemistry (IHC) and molecular study, as per WHO (2016) guidelines.

METHODS

This is a retrospective study conducted over a period of one and half years (July 2017 - December 2018), among 106 cases of ML. All the cases of ML were archived from the records of histopathology department in a tertiary care teaching hospital, Bhubaneswar, Odisha which is an oncology referral centre for Eastern India. The clinical history, radiological findings, biochemical and haematological parameters were taken into account. The haematoxylin and eosin stained slides and IHC slides were examined by three pathologists including the first author. An entire spectrum of IHC markers for lymphoma panel was done which included LCA, CD 20, CD3, CD4, CD8, CD138, CD5, CD10, BCL2, BCL6, MUM1, EMA, ALK1, CD15, CD30, Tdt, CD138, CD68, PAX5, c - MYC, Kappa and Lambda light chain and ki67. One year follow up of the patients was studied, post neoadjuvant therapy.

RESULTS

It was observed that among 106 cases of ML, HL was 26.42 %, much lower as compared to incidence of NHL (73.58 %), with a ratio of (1 : 2.78) (Table 1). The commonest type of HL was mixed cellularity (MC) type (57.14 %) followed by nodular sclerosis (NS) (35.71 %) and rest nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) (Figure 1). The age incidence of MC was bimodal with 68.75 % occurrence in paediatric population and 25 % in adults, similar findings were noted in case of NLPHL (showing equal incidence in childhood and elderly) and 70 % (7 cases) of NS type were adults in between second to third decade of life. In MC type males were more affected than females (3 : 1), whereas NS was more common in females, with male to female ratio of 1 : 2.33. All but two cases of MC type of HL were nodal in location. The extranodal sites of MC type of HL were stomach, large intestine (1 case each). One case of NLPHL was diagnosed as T cell histiocyte rich large B cell lymphoma (THRLBCL) variant according to WHO criteria based on combined IHC findings of NLPHL (CD20, CD3, CD4, CD23 positivity) as well as THRLBCL (CD3, CD8, CD68) positivity.

The NHL of B cell type comprised of mature B cell type (100 %) subcategorised into large cell type and small to intermediate cell type. The large cell type B cell NHL were the predominant type, the DLBCL being the commonest subtype. BL was seen in paediatric age, whereas DLBCL, THRLBCL and Plasmablastic lymphoma (PBL) occurred in aged (above 50 years). Rest belonged to the adult age group (Table 2). Nodal involvement was seen in (75.47 %) cases, cervical node being the commonest (32.07 %) site whereas extranodal involvement was seen in (24.53 %) cases (vertebra, stomach and central nervous system) (Table 3.a and 3.b). Amongst the DLBCL (53.85 %) majority were ABC type (35.90 %) than GCB type (17.95 %). One of the DLBCL of anaplastic variant occurred at extranodal site (second lumbar vertebra), showed positivity for LCA, CD20, PAX5, CD30 and negativity for CD15. Of all the ABC type one case showed double expression (positivity for BCL2 and c - MYC) and two cases of triple expression (positivity of BCL2, BCL6, c - MYC with ki67 - 90 %) were seen. One of the triple expression type of DLBCL occurred in central nervous system, cerebellar in location. Other large cell lymphomas were Plasma-Blastic Lymphoma (PBL) (2 cases), THRLBCL (one case) and high grade B cell lymphoma not otherwise specified (NOS) (1 case) with features intermediate between DLBCL and BL based on IHC findings of LCA, CD20, CD10 BCL2 and c-MYC positivity with 95% Ki67 labelling index. Both PBL occurred in elderly females and extranodal in

location (jejunum and stomach respectively). One of the PBL was positive for human immunodeficiency virus (HIV) infection. Both the cases of PBL were diagnosed based on positivity of CD138, Lambda chain, MUM1 and negativity of LCA and CD20. The gastric plasmablastic lymphoma died 3 months after diagnosis. The small to intermediate lymphoma were CLL / SLL (4 cases), gastric MALToma (2 cases), Mantle cell lymphoma (2 cases), follicular lymphoma (FL) (6 cases), BL (2 cases). The FL were further subcategorised into grade I (2 cases), grade II (2 cases), grade III (2 cases) based on the WHO criteria of morphology. All were seen in 30 - 60 years age group with male : female ratio of 1 : 1.5 and showed CD20 and BCL2 positivity and CD23, Cyclin D1 negativity. Grade I had less than 5 % centroblasts / follicles, with Ki67 12 %, grade II had greater than 75 % follicular pattern and 10 % centroblasts with Ki67 activity 40 % and grade III was having 20 % centroblasts and Ki67 of 45 % (Figure 2). One of the Grade II FL had a history of recurrence after six cycles of chemotherapy and had peritoneal spread along with splenomegaly. The grade III also showed recurrence with involvement of abdominal lymph nodes along with cervical lymph nodes. Both grade II and III thus presented with stage III category of FL. One of the BL cases was a 29-year male who had multifocal involvement, radiologically having terminal ileal, caecal and appendiceal thickening with moderate ascites. Biopsy from omentum, appendix, ileum and caecum revealed medium sized lymphoid cells with cMYC, CD10 and BCL6 positivity and 100 percent Ki67 activity. It showed bone marrow involvement, presented as stage IV disease. One of the cases of CLL / SLL, was a 57 year female, contrast enhanced computed tomography (CECT) and ultrasonography (USG) of abdomen showing heterogenous soft tissue attenuation enhancing mass lesion extending from epigastrium till umbilical region closely abutting pancreas measuring approximately (11.0 x 11.0 x 7.5) cm suspicious of gastrointestinal intestinal stromal tumour. USG guided biopsy from abdominal necrotic mass showed features of diffuse small cell lymphoma showing LCA, CD20, CD23 positivity, focal CD5 positivity and Ki67 index of 55 % confirming it to be a case of CLL / SLL with blastic transformation (Richter's syndrome).

The commonest subtype of T cell NHL was PTCL (8 cases; 10.26 % of NHL), presented with majority in extranodal sites (stomach, lung, liver and skin) and few multifocal in nature. The biopsy diagnosis was based on CD3 and CD4 positivity along with CD45RO positivity. The anaplastic large cell lymphoma (ALCL) was the second most common entity with four cases (5.48 % of NHL), the diagnosis of which was based on IHC profile of positivity for CD3, CD30 and EMA where as CD20, LCA, PAX5 were negative. Two cases showed ALK positivity whereas the other two showed ALK negativity. The ALK positive ALCL responded well to targeted chemotherapy. The precursor T cell lymphoma (T cell ALL), was diagnosed in a seven-year-old male child who presented with a mediastinal mass, showing stage IV disease with bone marrow involvement. IHC and flowcytometry both showed CD3, TdT and CD99 positivity. Site-specific T cell NHL included NK/T cell lymphoma (1 case), mycosis fungoides (2 cases) and EATL (one case). EATL diagnosis was based on the morphology of celiac disease in ileum with significant ileal ulceration and cutaneous metastasis, showing polymorphous population with few large Reed Sternberg (RS) like cells. IHC revealed CD3 positivity, though CD4 and CD8 were negative, thus final diagnosis was based on confirmation by TCR - gamma gene rearrangement (Figure 3). The patient died due to ileal perforation and peritoneal involvement. The cutaneous NHL were mycosis fungoides (2 cases) diagnosis of which was based on CD3, CD4 positivity and CD8 negativity along with typical epidermotropism by large cerebriform cells. One of them had significant dermal involvement. The sinonasal NK / T cell lymphoma was located in nasal cavity as a polypoid mass showing monotonous lymphoid cells showing angiotropism and angioinvasion with diffuse positivity for CD56 and CD3 negativity.

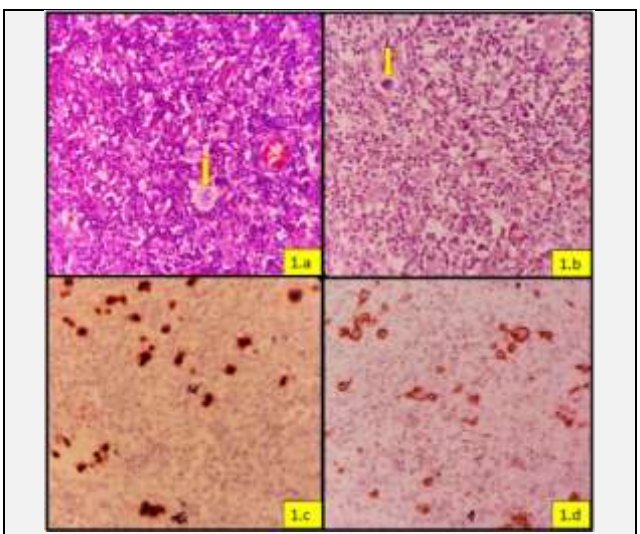

Figure 1. Various Types of Hodgkin Lymphoma with Immunohistochemical Stains

Figure 1: (1.a) Photomicrograph showing histomorphology of Hodgkin lymphoma of mixed cellularity type with classical R - S cells (arrowed) (H&E 400x), (1.b) Photomicrograph showing nodular sclerosis type of Hodgkin lymphoma with lacunar cells (arrowed) (H&E 400x), (1.c) CD 15 positivity for Hodgkin Reed Sternberg (HRS) cells (IHC 400x), (1.d) CD 30 membranous positivity with golgi accentuation for the HRS cells (IHC 400x).

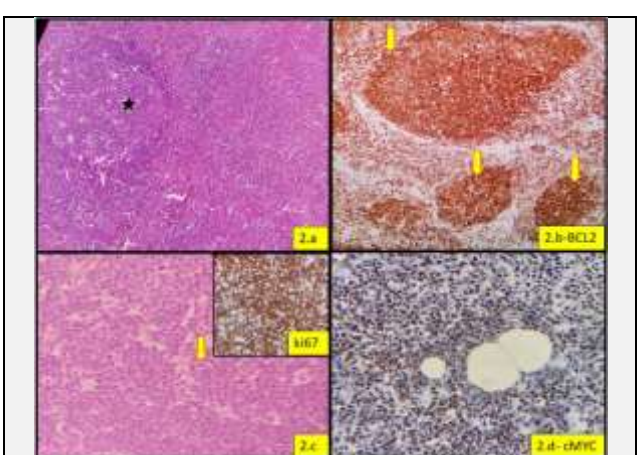

Figure 2. Various Types of B Cell Non-Hodgkin's Lymphoma with Immunohistochemical Stains

Figure 2: (2.a) Photomicrograph showing histomorphology of Follicular lymphoma showing predominant follicles (starred) (H&E, 400x), (2.b) Photomicrograph showing strong positivity of BCL2 in the neoplastic follicles (arrowed) (IHC 400x), (2.c) Photomicrograph of histology of Burkitt lymphoma showing starry sky appearance (H&E 400x) with 100 % ki 67 labelling index (inset) and (2.d) cMYC positivity (IHC 400x)

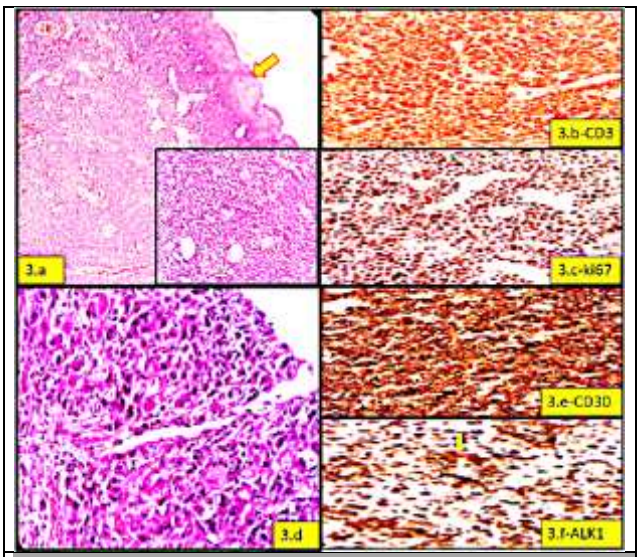

Figure 3. Various Types of T Cell Non-Hodgkin's Lymphoma with Immunohistochemical Stains

Figure 3a. Photomicrograph of enteropathy associated T cell lymphoma (EATL) in ileal biopsy (H&E 100x), showing malignant lymphoid cells infiltrating the epithelium and lamina propria with villous blunting (arrowed). (3.b) Diffuse and strong CD3 positivity for the neoplastic lymphoid cells in EATL (IHC 400x), (3.c) Ki67 labelling index of 85 % in EATL (IHC 400x), (3.d) Photomicrograph showing anaplastic large cell lymphoma (ALCL) (H&E 400x), (3.e) Diffuse and strong positivity for CD30 in ALCL (IHC 400x) and (3.f) ALK - 1 positivity with a pseudo - rosetted pattern in ALCL (arrowed) (IHC 400x).

Type of Lymphoma	Number of cases
1) Hodgkin lymphoma	**28 / 106 (26.42 %)**
a) Mixed cellularity	16 / 28 (57.14 %)
b) Nodular sclerosis	10 / 28 (35.71 %)
c) NLPHL	2 / 28 (7.14 %)
2) Non-Hodgkin's lymphoma	**78 / 106 (73.58 %)**
a) B cell NHL	60 / 78 (76.92 %)
i) Follicular lymphoma	6 / 78 (7.69 %)
ii) CLL / SLL	4 / 78 (5.13 %)
iii) Mantle cell lymphoma	2 / 78 (2.56 %)
iv) MALToma	2 / 78 (2.56 %)
v) DLBCL	42 / 78(53.85 %)
va) Germinal centre B type	14 / 78 (17.95 %)
vb) Post germinal centre B type	28 / 78 (35.90 %)
THRLBCL	4 / 78 (5.13 %)
vi) Plasmablastic lymphoma	2 / 78 (2.56 %)
vii) Burkitt lymphoma	2 / 78 (2.56 %)
b) T cell NHL	18 / 78 (23.08 %)
i) PTCL	8 / 78 (10.26 %)
ii) ALCL	4 / 78 (5.13 %)
iii) NK / T - CELL	2 / 78 (2.56 %)
iv) T - ALL (lymphoblastic)	1 / 78 (1.28 %)
v) Mycosis fungoides / CTCL	2 / 78 (2.56 %)
vi) EATL	1 / 78 (1.28 %)
Total number of cases	**106**

Table 1. Incidence of Various Types and Subtypes of Malignant Lymphomas (n=106)

Type of Lymphoma	Age of Incidence (in Years)		
	Paediatrics (0 – 14 yr.)	Adult (15 – 50 yr.)	Elderly (51 – 90 yr.)
1) Hodgkin lymphoma			
a) Mixed cellularity	11 / 28 (39.28 %)	4 / 28 (14.28 %)	1 / 28 (3.57 %)
b) Nodular sclerosis		7 / 28 (25 %)	3 / 28 (10.71 %)
c) NLPHL	1 / 28 (3.57 %)		
2) Non Hodgkin lymphoma			
a) B cell NHL			
i) Follicular lymphoma		4 / 78 (5.12 %)	2 / 78 (2.56 %)
ii) CLL / SLL			4 / 78 (5.13 %)
iii) Mantle cell lymphoma		2 (2.56 %)	
iv) MALToma		2 (2.56 %)	
v) DLBCL			
va) Germinal centre B type		1 (1.28 %)	13 (16.67 %)
vb) Post germinal centre B type		3 / 78 (3.85 %)	25 / 78 (32.05 %)
THRLBCL			4 / 78 (5.13 %)
vi) Plasmablastic lymphoma			2 / 78 (2.56 %)
vii) Burkitt lymphoma	1 / 78 (1.28 %)	1 / 78 (1.28 %)	
b) T cell NHL			
i) PTCL			8 / 78 (10.25 %)
ii) ALCL			4 / 78 (5.12 %)
iii) NK / T - Cell		2 / 78 (2.56 %)	
iv) T – ALL (lymphoblastic)		1 / 78 (1.28 %)	
v) Mycosis fungoides / CTCL		2 / 78 (2.56 %)	
vi) EATCL			1 / 78 (1.28%)
Total number of cases	**13 / 106 (12.26 %)**	**29 / 106 (27.35 %)**	**64 / 106 (60.38 %)**

Table 2. Age Wise Distribution of Malignant Lymphomas (n=106)

Type of Lymphoma	Lymph Node Involvement					
	Cervical	**Inguinal**	**Axillary**	**Mediastinal**	**Retroperitoneal**	**Multifocal**
1) Hodgkin lymphoma						
a) Mixed cellularity	9		3	1		1
b) Nodular sclerosis	7		3			
c) NLPHL	1		1			
2) Non Hodgkin lymphoma						
a) B cell NHL						
i) Follicular lymphoma	1	1	3		1	
ii) CLL / SLL		1	2		1	
iii) Mantle cell lymphoma	1		1			
iv) MALToma						
v) DLBCL						
va) Germinal centre B type	4	4	6			
vb) Post germinal centre B type	7	3	4			
THRLBCL	1	1			1	1
vi)Plasmablastic lymphoma						
vii) Burkitt lymphoma		1				1
b) T cell NHL						
i) PTCL	2					4
ii) ALCL	2				2	
iii) NK / T - CELL			1			
iv) T – ALL (lymphoblastic)				1		
v) Mycosis fungoides / CTCL						
vi) EATL						
Total number of cases	**34 / 106 (32.07 %)**	**10 / 106 (9.43%)**	**24 / 106 (22.64 %)**	**2 / 106 (1.89 %)**	**4 / 106 (3.77 %)**	**6 / 106 (5.66 %)**

Table 3a. Nodal Site Wise Distribution of Malignant Lymphomas (n = 80)

Type of Lymphoma	Extranodal Site of Involvement							
	Stomach	**Small Intestine**	**Large Intestine**	**Sino-nasal**	**CNS**	**Testis**	**Lungs**	**Skin**
1) Hodgkin lymphoma								
a) Mixed cellularity	1 / 28 (3.57 %)		1 / 28 (3.57 %)					
b) Nodular sclerosis								
c) NLPHL								
2) Non Hodgkin lymphoma								
a) B cell NHL								
i) Follicular lymphoma								
ii) CLL / SLL								
iii) Mantle cell lymphoma	1 / 78 (1.28 %)	1 / 78 (1.28 %)						
iv) MALToma								
v) DLBCL								
va) Germinal centre B type								
vb) Post germinal centre B type	5 / 78 (6.41 %)		3 / 78 (3.85 %)	2 / 78 (2.56 %)	2 / 78 (2.56 %)	1 / 78 (1.28 %)	1 / 78 (1.28 %)	
THRLBCL								
vi) Plasmablastic lymphoma	1 / 78 (1.28 %)	1 / 78 (1.28 %)						
vii) Burkitt lymphoma								
b) T cell NHL								
i) PTCL	5 / 78 (2.56 %)							
ii) ALCL								
iii) NK / T- CELL				1 / 78 (1.28 %)				
iv) T-ALL (lymphoblastic)								
v) Mycosis fungoides								2 / 78 (2.56 %)
vi) EATL			1 / 78 (1.28 %)					
Total no of cases	**10 / 106 (9.43 %)**	**2 / 106 (1.89 %)**	**5 / 106 (4.72 %)**	**3 / 106 (2.83 %)**	**2 / 106 (1.89 %)**	**1 / 106 (0.94 %)**	**1 / 106 (0.94 %)**	**2 / 106 (1.89 %)**

Table 3b. Extranodal Site Wise Distribution of Malignant Lymphomas (n = 26)

DISCUSSION

Classification of ML has changed over the years from 2008 to 2016 with inclusion of many IHC and molecular markers, prognostically significant to the oncologist.[21-22] Thus the study attempts to document ML based on WHO classification (2016) guidelines. Among the patients HL comprised of 26.42 % and ratio of NHL to HL 2.78 : 1. Similar to other studies MC is the commonest subtype (57.14 %) of total HL, followed by NS type (35.71 %).[23] On the contrary European, United states of America showed NS type as the commonest subtype.[21, 23, 24, 25, 26] With regard to specific subtype of B cell NHL, DLBCL topped the chart accounting to 53.85 % of all NHL and 70 % of B cell NHL, followed by FL (7.69 % of all NHL and 10 % of B cell NHL). [23, 24, 25, 26] Many Indian studies show similar incidence of DLBCL varying from 25 – 35 %. [21, 27] It was found that FL occurred in higher proportion in western studies.[25, 28] Commonest nodal site of NHL was in cervical lymph node, followed by axillary, inguinal, multifocal, retroperitoneal and lastly mediastinal lymph nodes.[23] A study conducted by Chakrabarti et al also showed that in NHL major lymph node groups involved were most common in cervical (78.95 %), followed by axillary (55.3 %) and inguinal (39.47 %).[24] Extranodal sites of B cell NHL were mostly in stomach (7 cases) followed by large intestine (3 cases), small intestine (2 cases), sinonasal (2 cases), CNS (2 cases), testis and lung (1 case each), constituting 30 % of B cell NHL. Other studies showed small intestine being the most commonly affected site followed by tonsil, stomach etc.[23] Further subtyping of DLBCL showed triple, double expression and NOS category showing worse prognosis. Similarly, FL was categorised into three grades based on which the prognosis was variable as grade II and III had recurrence and presented as stage III tumours. [29] Plasmablastic lymphomas presented with stage IV disease showing bone marrow involvement similar to Burkitt lymphoma. [29] PTCL with multiorgan involvement and EATL had worse prognosis, due to disseminated spread. The ALK positive type of ALCL had much better prognosis than the ALK negative which responded well to targeted chemotherapy. Total of five cases died in one year follow up period which included both cases of plasmablastic lymphomas (gastric and jejunal), gastric PTCL (1 case), gastric DLBCL (1 case) and ileal EATL (1 case) mainly due to systemic complications. All these ML had high proliferative index and carry very poor prognosis.[29]

CONCLUSIONS

Epidemiology of malignant lymphoma is variable in developing countries like India and much different from developed countries showing male predominance and nodal site preponderance. NHL of B cell type is the predominant type of lymphoma, commonest type being DLBCL followed by FL, CLL / SLL, with equal incidence of mantle cell lymphoma and MALToma. PTCL is the commonest type of T cell NHL followed by ALCL, showing predilection extranodal site. HL incidence is much lower that NHL but showed predominance in females occurring more in paediatric population. Prognosis of different types lymphomas was significantly variable with HL responding well to chemotherapy with complete remission. MALToma, CLL / SLL, FL and mantle cell lymphomas had intermediate prognosis with few cases showing recurrence after completing chemotherapy. DLBCL, particularly anaplastic type, triple expression type and extra nodal type as well as PBL and BL carry grave prognosis. Similarly, T cell NHL

carries worse prognosis than B cell NHL, and had much diagnostic difficulty with multiorgan involvement and need for specific molecular diagnosis for institution of proper neoadjuvant therapy.

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