BJMHR
British Journal of Medical and Health Research
Journal home page: www.bjmhr.com

Trends in the incidence of Childhood Lymphoma Encompassing Pediatric Population from western Uttar Pradesh

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ABSTRACT

Progress in the diagnosis and treatment of neoplasm in children in past few decades is one of the most gratifying achievement in the field of oncology. Childhood lymphomas are rare paediatric malignancy characterized by abnormal growth of lymphocytes. Aims and Objectives of this study was to describe the epidemiology of childhood cancer in western Uttar Pradesh, a state in Northern India, that would serve as a National reference source and will act as a seminal to spawn new research in the field of childhood lymphomas. The study evaluated a total of 252 cases of pediatric tumors over a period of seven years, including patient of 0-12 years of age group; attending the out-patients and in-patients of Jawaharlal Nehru Medical College (tertiary care centre), Aligarh, with the complaints of tumor associated sign and symptomsLymphoma being 3rd most common childhood malignancy in our study comprised a total of 15 cases, that included 9 cases of Hodgkin's Lymphoma (HL) and 6 cases of Non Hodgkin's Lymphoma (NHL). It accounted for 6% of total neoplasm and 12.5% of all pediatric malignancies. The mean age of occurrence was 8.1 years with a slight male predilection.

Keywords: Pediatric, Lymphoma, Hodgkin's disease, Tumor

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Received 27 June 2016, Accepted 07 August 2016

Please cite this article as: Qadri S *et al.*, Trends in the incidence of Childhood Lymphoma Encompassing Pediatric Population from western Uttar Pradesh. British Journal of Medical and Health Research 2016.

INTRODUCTION

Cancer in children and adolescents is rare and biologically very different from cancer in adults.[1] In India cancer is the 9th common cause for the deaths among children between 5 to 14 years of age.[2] An estimated 160,000 new cases of children below 15 years of age are diagnosed with cancer each year worldwide, with 90,000 deaths attributed to cancer.[3] In India approximately 45,000 children are diagnosed with cancer every year.[4] Presently only population-Based Cancer Registries (PBCR) under the National Cancer Registry Programme have been running actively in our country, although the age adjusted incidences of most of adult cancers are very high, there are no published data on childhood cancers.[5] The proportion of childhood cancers relative to all cancers reported by Indian cancer registries varied from 0.8% to 5.8% in boys, and from 0.5% to 3.4% in girls.[6] Lymphomas are cancers of a certain type of white blood cell (lymphocyte) that can arise in any body site where lymphocytes are found such as bone marrow, lymph nodes, spleen, intestines, and other lymphatic system. Pediatric lymphomas are the third most common malignancy in children and accounts for 13% of all childhood cancers.[7]

Hodgkin's lymphoma (HL) is an uncommon disorder with heterogeneous clinical, histologic and epidemiologic characteristics. It is a cancer of lymphoid tissue, often involving the lymph nodes in the neck, chest, or abdomen originating from B lymphocyte and less common from T lymphocyte. Hodgkin's Lymphoma is characterized by the presence of binucleated and multinucleated giant cells, known as Red-Stenberg cells, in the background of numerous reactive lymphocyte.[8] There are two major types of HL: Classic HL which is the most common of all and shows the same histologic picture as describe above, while the other type is Nodular Lymphocyte Predominant (NLPHL), which is characterized by the so called "Popcorn cells." This type is rare and tends to be slower growing than the classic form.[9] The most common subtype of HL, based on different studies in the most Asian countries such as Iran, Korea, Thailand, Japan is Mixed Cellularity and relative paucity of Nodular Sclerosis subtype, particularly in males.[10] HL is found to be a curable disease in most patients. [11]

Non-Hodgkin lymphoma is a heterogeneous group of B-cell and T-cell neoplasm that arise primarily in the lymph nodes with varied clinical and biologic feature. Among B-cell lymphomas, diffuse large B cell lymphoma (DLBCL) is the most common non-Hodgkin's Lymphoma representing approximately one third of all Non-Hodgkin's Lymphomas worldwide.

MATERIALS AND METHOD

A retrospective and prospective study of paediatric tumours was commenced during period from January 2005 – January 2012. All children with cancer, aged 0 to 12 years attending the out patients and in patients departments of paediatrics, surgery and orthopaedic surgery at Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh Muslim University, Aligarh, who presented with the tumour or with the tumour associated sign and symptoms diagnosed by means of histological or cytological examination during that period, were included in the study. The case records were analyzed to show the descriptive clinical profile of the patients. The profile of childhood cancer was studied focusing on the prevalence of tumours according to nature of lesions (benign vs. malignant), most common site of involvement of particular tumour, age, sex, and common or uncommon for that age. The material for this study was obtained from following sources: Retrospective study of histopathological sections of cases of paediatric tumours in department of pathology from January 2005 – July 2009, as the gross specimen of those tumours were not available the descriptions were obtained from the original forms of the respective cases. Fresh sections were taken from the paraffin blocks and were stained. For prospective study, histopathological sections were obtained from the gross specimen of paediatric tumours that were sent to histopathology section in the department of pathology, from August 2009 – January 2012. Haematoxylin and Eosin stain were used for staining histopathological sections, special staining and immunostaining were done as per requirement.

RESULTS AND DISCUSSION

The study included a total of 252 confirmed cases of paediatric tumours over a period of seven years. Soft tissue tumours 90 cases (35.7%) accounted maximum number, followed by Bone and Cartilage tumours 28 (11.1%), Leukaemia 24 (9.5 %), Brain tumours 22 (8.7%), Round cell tumours including Ewing's sarcoma, Retinoblastoma and Neuroblastoma etc 20 (8%), Genital tumours 18 (7.1%), Lymphomas 15 (6%), Renal tumours 14 (5.6%), Gastrointestinal tumours 2 (1.2%), while the miscellaneous category constituted 18 (7.1%). Lymphomas (Hodgkin's and non-Hodgkin) accounted for 6% of total and 12.5% of malignant paediatric neoplasm studied. Although all of the case presented with painless enlargement of various lymphnode, however 15% of case also had fever. 5 cases were seen in 0-6 years while 10 cases were between 7-12 years age group. Mean age of occurrence was observed to be 8.1 with a slight males predilection years. There were a total of 9 cases of Hodgkin's disease and 6 cases were of non Hodgkin's lymphoma. Hodgkin's lymphoma (9/15 cases) accounted for 3.6% of malignancies in present study. Mean age of occurrence was 8.9 years with slight male preponderance, M:F ratio being 1.3 : 1. We found the following variants of HD in our study, *(1) Mixed cellularity* (4/9 cases): Histopathology

revealed complete effacement of lymphnode architecture with large number of eosinophils, plasma cells and and atypical mononuclear cells (Hodgkin's cells), RS cells and lymphocytes (figure 1a). *(2) Nodular sclerosis* (4/9 cases): lymphnode microscopy revealed capsular invasion and distortion of normal architecture with broad fibrocollagenous band separating lymphoid tissue in well defined nodules, many lacunar cells and few mononuclear RS cells were observed (figure 1b). Von Gierke staining revealed broad collagen bands (hyalinization and sclerosis), however loss of LN architecture was much evident by reticulin staining. *(3) Lymphocyte depletion* (1/9 case): Hematoxylin and eosin stain of lymphnode section showed complete architectural distortion with atypical pleomorphic histiocytes, few atypical RS cells and cellular areas of lymphocytes alternating with hypocellular areas, almost completely devoid of lymphocytes, focal areas of fibrosis and necrosis were also seen. Mononuclear and RS cells were CD 15 and CD 30 positive in all the cases (figure 1c)

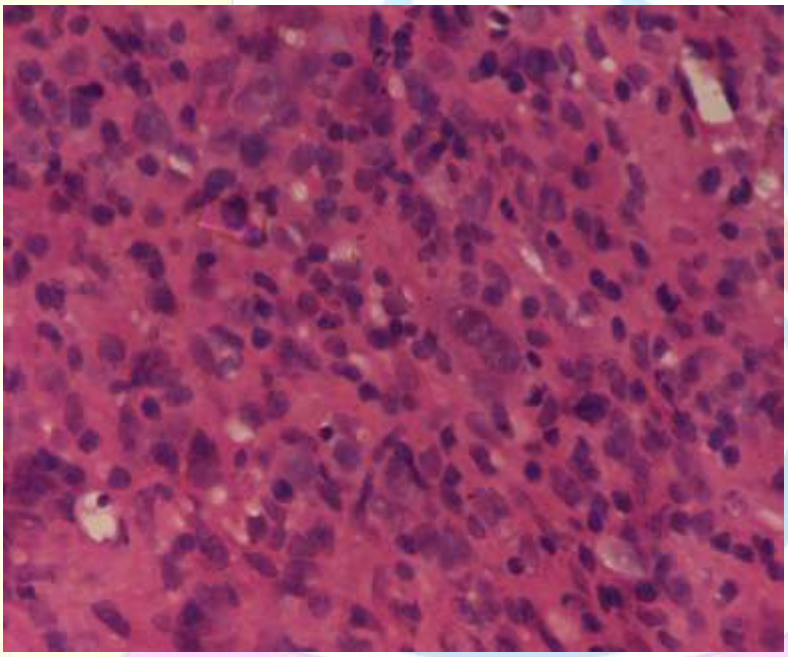

Figure 1a: Hodgkins lymphoma- Mixed cellularity: Showing mononuclear and binuclear Reed Sternberg cells (H& E x 400).

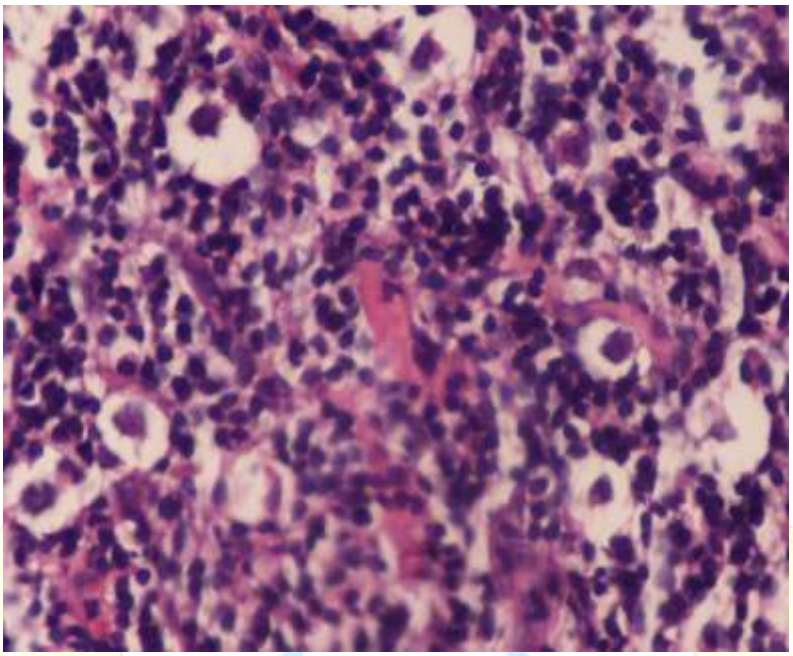

Figure 1b.**Hodgkins lymphoma- Nodular sclerosis: Showing lymphoid cell population and lacunar cells (H& E x400).**

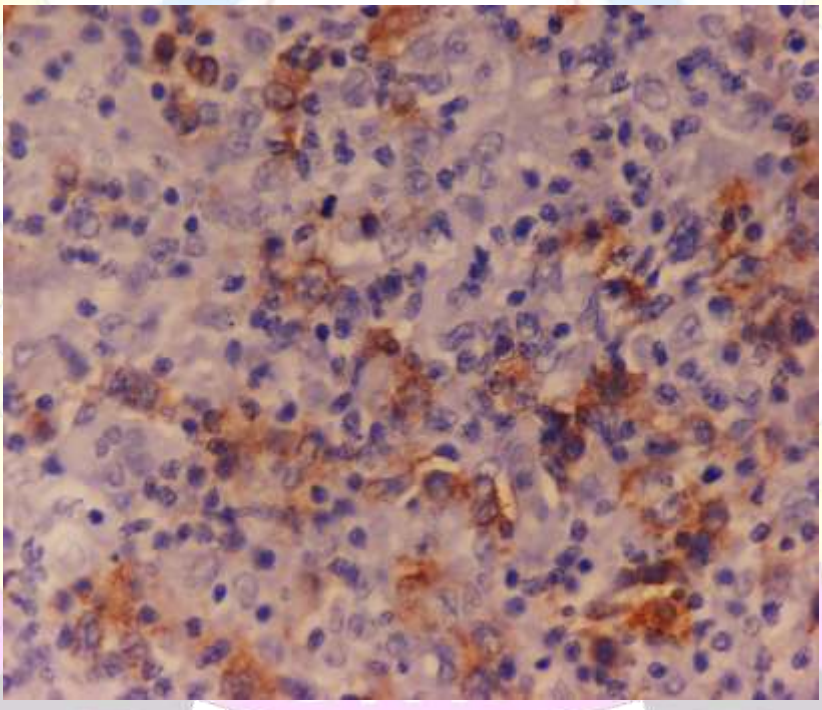

Figure 1c: Hodgkins lymphoma: Mononuclear and Binuclear (RS) cells showing positivity for CD30. (IHC, x 400)

Non Hodgkin's lymphoma (6/15 cases) accounted for 5% of total malignancies with mean age of occurrence being 7.4 years. Equal incidence was observed in both the sexes. The following variants of NHL were encountered, *(1) Diffuse large B cell Lymphoma [DLBCL*](4/15 cases) in which histopathology of lymphnode revealed diffuse pattern of growth with large tumor cells with opened up chromatin and prominent nucleoli (figure 2a). *(2) Small Lymphocytic Lymphoma [SLL]* (2/15 cases), on microscopy complete effacement of

lymphnode architecture was seen with monotonous proliferation of lymphocytes with clumped chromatin (figure 2b). The tumour cells were positive for leucocyte common antigen (CD 45) (figure 2c), CD 19 and CD 20. While CD 5 and CD 23 were positive in SLL/CLL, DLBCL showed negative immunostaining for these antigens.

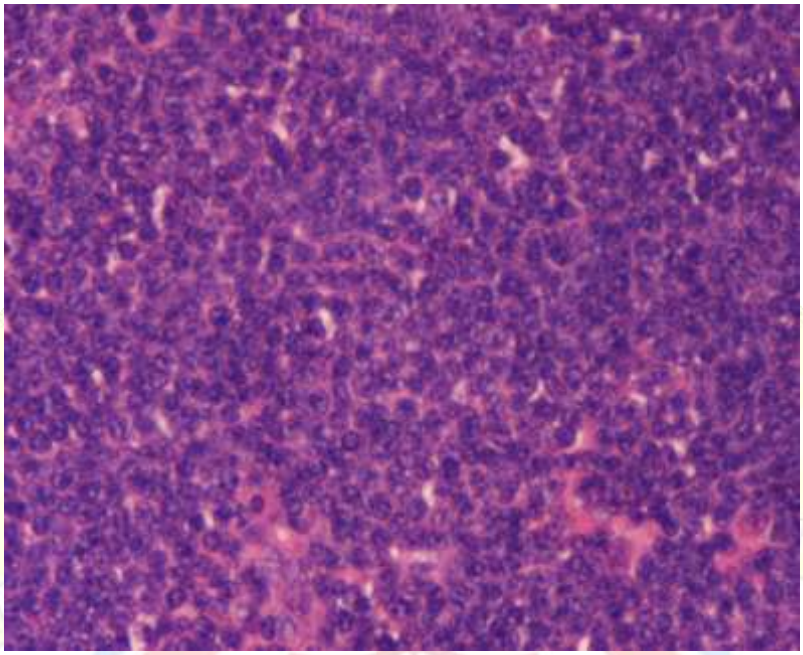

Figure 2a: Non Hodgkins lymphoma-: Small lymphocytic lymphoma (SLL) Showing solid pattern of growth of monotonous cell population, intermediate sized cells, prominent nucleoli seen(H& E, X 100).

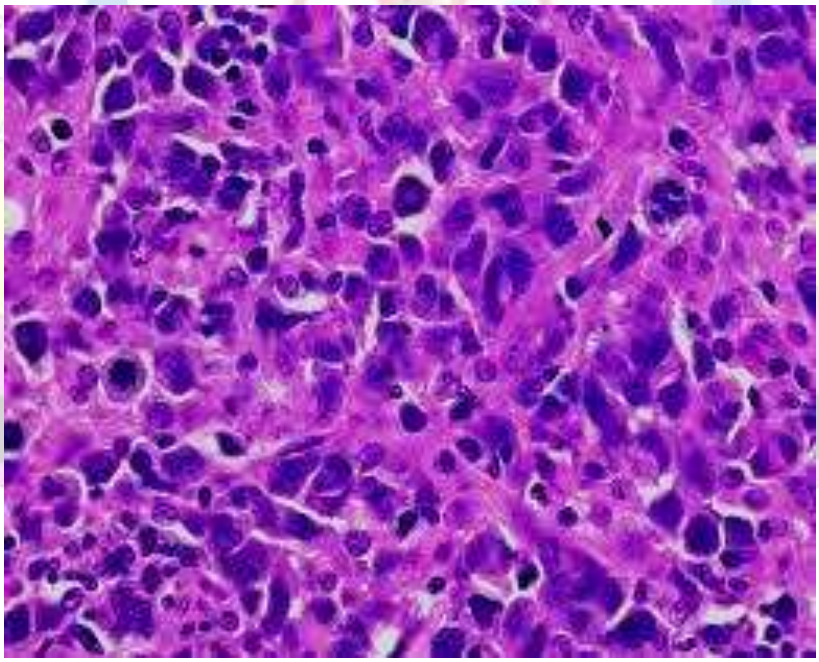

Figure 2b: Non Hodgkins lymphoma- Diffuse large cell: Showing solid pattern of growth of monotonous cell population, intermediate sized cells, with a high mitotic count (H& E, x400).

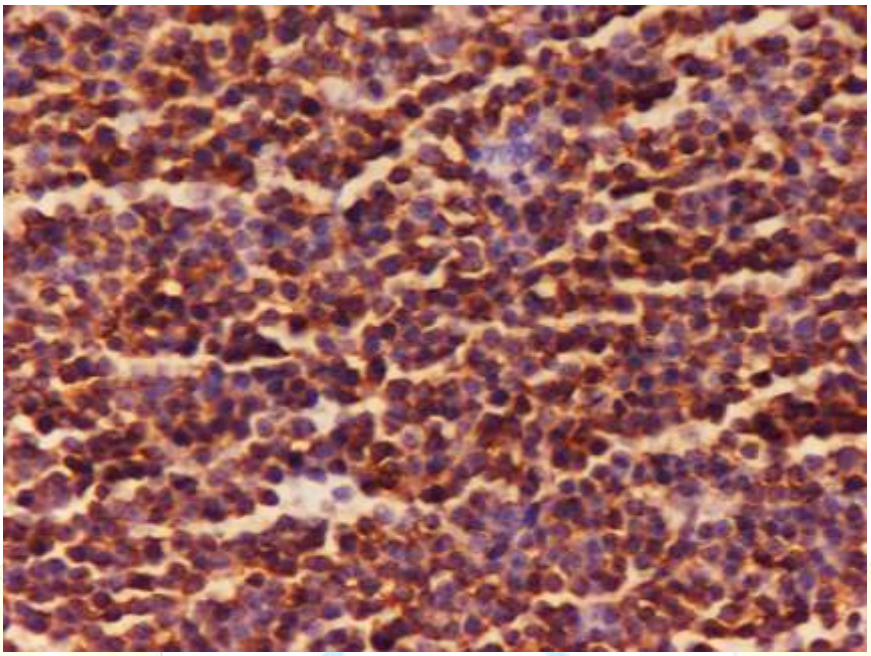

Figure 2c: Non Hodgkins lymphoma (SLL): Showing strong CD-45 positivity (IHC, X 100)

Lymphoid malignancy is a remarkable disease because of its difference in epidemiology and etiology in different areas around the world. Several features of the epidemiology of lymphoid malignancy particularly stand out. The overall lymphoid malignancy incidence in Asian countries is relatively low. Histopathological subtypes of lymphoma are different in eastern and western countries and generally similar among Asian countries. Lymphomas stood, third most common tumour of all malignancies and second most common solid neoplasm in our study. It comprised of 12.5% of total malignancies. This finding was similar to that observed by Hudson et al.1996,[12] Arora et al. 2009,[4] Kaatsch et al. 2010, [13] and in variance to the observation of Jabeen et al. 2010[14] and Shah et al. 2000,[15] as both of them found lymphoma as the most common tumor, being 24.2% and 26.1% of all childhood tumours they studied respectively. In our study, Hodgkin's lymphoma were more commonly seen than non Hodgkin Lymphoma, ratio being 1.5:1, a finding comparable to the study of Hazarika et al. 2014[5] who found Hodgkin's lymphoma in 8.2% and non Hodgkin's lymphoma in 4.8% of children. However our study was in total variance to that reported by Shah et al.2000,[15] who found NHL to be more prevalent than HL. Slight male predominance was seen only in HLs in our study, much similar to what observed in study of Gurney JG et al. 2006,[16] who found lymphoma to be predominant in male (more in case of HL than NHL), however the study conducted by Shah et al. 2000,[14] reported M : F ratio as, 5.6 : 1 and 6.3 : 1 in cases of NHL and HL respectively.

Paediatric Hodgkin's lymphoma is currently one of the most curable childhood malignancies. With an incidence of 0.64 per 100,000 US children younger than 15 years, HL accounts for

over half of all lymphomas, which are the third most common cancer in children after leukemias and brain tumours. Incidence of HL is roughly the same in Asians as in the US. In developing countries Hodgkin lymphoma has been seen to have a high male to female ratio, younger age at presentation, a high proportion of patients in advanced stage of disease, constitutional symptoms, and predominance of Mixed cellularity histologic type. The results of treatment appear to be comparable to the results attained in developed nations. [17] . Among Indian children, HL is the fourth more common malignancy after acute lymphoblastic leukemia (ALL), brain tumours and retinoblastoma. HL cases under the age of 5 years are seen in about 20% from developing countries vs. about 5% in western countries.[18] Paediatric HL shows a slight male predominance in Western countries, with M: F ratio of about 1.5:1, however male predominance is much higher in

developing countries with M: F ratios being 2.5:1 to8.[18] Most cases of childhood HL are of nodular sclerosis subtype in developed countries, whereas in developing countries, mixed cellularity is the commonest subtype, accounting for about 60% of the cases.[19] Pre-existing immunodeficiency, either congenital or acquired, increases the risk of developing HL. The increased incidence of HL in AIDS is approximately 3 to 10 folds. The most common presentation of HL in children is a painless cervical or supraclavicular lymphadenopathy, usually unilateral, firm and rubbery, which may become fluctuant over time. HL arises in lymphoid tissue and spreads to adjacent lymph node areas. Haematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic B-symptoms. B symptoms include unexplained persistent fever (above 38^{o}C), night sweats, weight loss >10% of body weight in the previous six months. Hodgkin's lymphoma accounted for 7.5% of all malignancies in present study. The variants of HL encountered in our study were, Mixed Cellularity and Nodular Sclerosis in an equal frequency followed by Lymphocyte Depletion and Lymphocyte Predominant. This finding varied from those of Hudson et al.1996,[12] who found Nodular Sclerosis as the most common variant followed by Mixed Cellularity and Lymphocyte Depletion. Hodgkin's and RS (H-RS) cells of classical HL are typically CD15 positive, CD30 positive while T cell and B-cell-associated antigens are and leukocyte common antigen (CD45) negative. In contrast to classical HL, the tumour cells of NLPHL, also called lymphocytic histiocytic (L&H) cells or "popcorn cells", are characterized by a complete or nearly complete B cell phenotype, CD45 positivity, while CD15 and CD30 are negative.

Paediatric Non-Hodgkin lymphomas (NHLs) differ from their adult counterpart in that the Low Grade Follicular Lymphomas seen in adults are exceedingly rare in children. Most of the lymphomas in children are rapidly growing and aggressive and present with wide spread

dissemination at the time of diagnosis.[2] Clinical presentation of NHLs correlate well with their rapid growth and doubling time. Majority of the patients will have widespread disease involving bone marrow and/or central nervous system.[1,2] Patients with precursor T cell lymphoblastic lymphomas usually present with a mediastinal mass, often accompanied by pleural effusion. The lymphadenopathy is usually supra-diaphragmatic. Patients may present with pain, dysphagia, dyspnea, swelling of neck, face and upper limbs due to superior vena-caval obstruction, hepato-splenomegaly may occur but abdominal involvement is rare. Bone marrow involvement is common and CNS involvement though rare may present as cranial nerve palsy or pleocytosis of cerebrospinal fluid.[20] Paediatric NHLs are divided into three major histological categories: Lymphoblastic lymphoma, Small non cleaved cell lymphoma and the Large cell lymphoma. The Revised European American Lymphoma classification (REAL) has been devised to classify lymphomas based on histology, immunology and genetic features.[4] The small non cleaved cell lymphomas are classified into Burkitt's and Burkitt's like lymphomas, lymphoblastic lymphomas are categorized as precursor T and precursor B type, while large cell lymphomas are divided into large B and large T cell type. The majority of large T cell lymphomas are CD30+ Anaplastic large cell lymphomas (ki-1). Burkitt's lymphoma, Burkitt's like lymphoma and about half of large cell lymphomas in children are of B cell origin, they express surface immunoglobulin of IgM type associated with kappa or lambda chain and B cell specific antigens CD19 and CD20. T cell lymphoblastic lymphomas are histologically similar to acute lymphoblastic leukemia. Immunologically, they are of precursor T cell antigen and express CD7, CD5, CD1, CD3, CD4, CD8 and CD2. Non Hodgkin lymphoma, accounted for 5% of all malignancies studied in our study less than that observed by Hazarika et al. 2014,[5] who found it to be 10%. The variants of NHL encountered in present study were, DLBCL followed by SLL, while Hazarika et al. 2014,[5] observed only DLBCL in their study. Sunland et al. 1996,[21] found small non cleaved cell lymphoma to be the most common, they also observed abdomen (31.4%) as the most common site for these lymphomas, followed by head and necuk (29%), while we found cervical LN to be most commonly involved organ.

In case of Hodgkin's lymphoma, risk adapted combined modality therapy is the standard of care in favourable and unfavourable early disease. Chemotherapy alone protocols are advocated by some groups, and show similar outcome, although isolated reports favour additional field radiotherapy. Interim and post-therapy Positron Emission Tomography (PET) is emerging as a tool to avoid radiation or to intensify therapy. Management of NHL is best carried out in specialized centres where physicians are familiar with the management of these tumours. Patients presenting with extensive disease may have a number of complications that

require management prior to the initiation of specific chemotherapy treatment. In the developed countries, the survival of childhood cancers is better than developing countries.[1,22,23] Also, in low and middle income countries, 56% of the cases and 64% of the deaths occur each year due to limited access to curative treatment including the lack of availability of common chemotherapeutic agents, high cost of treatment, late stage at presentation, and limited radiotherapy and surgical resources.[1,22] In addition, even when adequate oncologic treatments are available, disparities in education and socioeconomic conditions, coupled with inefficient or suboptimal health care delivery, result in poor outcomes for children diagnosed with cancer in low and middle income countries.[24]

CONCLUSION

Collaborative effort of Pediatric oncologists and a host of oncology specialists with insight into childhood lymphoma ensure its timely detection, sub-typing and early treatment of the disease, when the chances for cure are best. Ascertaining the clinic-pathological profile of childhood lymphoma in our population is essential for allocation and management of resources for this small but important group of patients. This type of analysis shed light on the pattern of care and necessitates the identification of socio-demographic determinants responsible for treatment compliance in childhood cancers.

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