

Primary Extranodal Non-Hodgkin's Lymphoma: An Observational Study at a Tertiary Care Teaching Centre in Northern India

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ABSTRACT

Introduction: Extranodal Non-Hodgkin's Lymphoma (NHL) constitutes approximately one fourth of all NHL. The data regarding extranodal NHL from India is however limited.

Aim: To evaluate the epidemiological and histomorphological patterns of extranodal NHL in a tertiary care institute in Northern India.

Materials and Methods: The retrospective observational study was conducted on data of biopsy sections retrieved from the archives for a period of four years (January 2016 to December 2019), 130 extranodal NHL cases (90 males, 40 females) that were analysed for histological features and immunohistochemical subtype. All statistical analysis was done by Statistical Package for Social Sciences (SPSS) software. The values were represented in number, percentage, mean and ratio.

Results: Total of 362 cases of NHL were reported. Out of which, 130 (36%) cases were of extranodal NHL. Male to female ratio being was 2.25:1. Mean age of presentation was 38.5 years. Paediatric

cases constituted (32/130; 24.6%) cases. Head and neck was the most common site (52/130; 40%) followed by Gastrointestinal Tract (GIT) (21/130; 16.2%) and central nervous system (13/130; 10%). Amongst the paediatric cases, head and neck (11/32; 34.4%) was the most common site, followed by GIT (8/32; 25%). Amongst head and neck lymphomas, nasal cavity and Waldeyer Ring were the most common sites followed by orbit and oral cavity. Common sites among the GIT lymphomas were stomach, small intestine and large intestine. The B-cell NHL constituted 81/130 (62.3%), T-cell NHL 20/130 (15.4%) and NHL (Unclassified) were 29/130 (22.3%). Amongst B-cell type NHL, Diffuse Large B Cell Lymphoma (DLBCL) was the most common subtype.

Conclusion: Extranodal NHL diagnosis is challenging due to morphological similarities with non haematopoietic tumours. Lineage determination by Immunohistochemistry (IHC) serves as the key to diagnosis. In our population, head and neck was the most common site, with B-cell NHL being the most common subtype.

Keywords: Anaplastic large cell lymphoma, Central nervous system, Diffuse large B-cell, Immunohistochemistry, Paediatric lymphoma

INTRODUCTION

The Non Hodgkin's Lymphoma (NHL) is a group of lymphoproliferative disorders arising in lymph nodes with heterogeneous, histological, and clinical characteristics [1]. At least one-quarter of NHL arise from tissues other than lymph nodes and even from sites, which usually do not contain lymphoid tissue. These groups are referred to as primary Extranodal Lymphomas (pENL) [2,3]. Various criteria have been proposed by different authors in the past, to categorise this entity [4,5].

In the recent years, the incidence of extranodal lymphoma is increasing, particularly at anatomical sites like central nervous system, GIT and the skin. This may be attributed to immunosuppressing diseases like Acquired Immunodeficiency Syndrome (AIDS) or immunosuppressive treatments, infections such as *Helicobacter pylori*, *Chlamydia psittaci*, *Borrelia burgdorferi*, and *Campylobacter jejuni*, autoimmune disorders and environmental factors also contribute to rise in incidence [6]. Interestingly, extranodal NHL's have been reported in almost every site of the body such as GIT, head and neck, central nervous system, bone, testis, skin, thyroid, breast, and orbit [7-15]. Diagnosis of extranodal lymphoma is a frequent challenge to the pathologists, due to their morphological mimics, molecular alteration, and clinical presentations.

This study was undertaken to ascertain the prevalence, anatomic site distribution and histomorphological subtypes of extranodal NHL from a tertiary care teaching institute in North India. In addition, the study also aims at highlighting the problems in the histopathological

diagnosis and role of IHC in arriving at a correct diagnosis in cases of difficulty.

MATERIALS AND METHODS

This retrospective observational study was conducted in Department of Pathology, King George's Medical University, Lucknow, India. Data of extranodal lymphoma was retrieved from archives for period of four years from January 2016 to December 2019. Demographic data, anatomic site and histopathologic subtypes were recorded in detail. Paraffin block was retrieved for those cases which were not classified and detailed panel of IHC was performed using a panel of antibodies depending on the morphology.

Study Procedure

An Immunohistochemical analysis was performed manually on the paraffin embedded tissue sections by using a panel of monoclonal antibodies. Antigen retrieval was done by pretreatment of paraffin sections by heating in an antigen retrieval system in 0.01 M citrate buffer (pH=6.0). Two panels of antibodies were used for IHC. First panel was used to rule out some site and age specific tumours. The panel included vimentin, pan cytokeratin, Leukocyte Common Antigen (LCA), desmin, myogenin, CD 99, synaptophysin, chromogranin, Octamer-Binding Transcription Factor 4 (OCT4) and Epithelial Membrane Antigen (EMA). A second panel of antibodies were used to subtype lymphoma when the diagnosis of lymphoma was confirmed which included CD3, CD4, CD5, CD8, CD19, CD20, CD23, CD10, CD15, CD30, CD99, CD56, B-cell lymphoma 2 (Bcl2),

Bcl6, Terminal Deoxynucleotide Transferase (Tdt), Anaplastic Lymphoma Kinase-1 (ALK-1), cyclinD1, Ki67 and EMA and CD56. Molecular diagnostic techniques such as cytogenetics/fluorescence in-situ hybridisation were not performed in any of the cases due to lack of facilities.

Since the clinical definitions of extranodal lymphoma are variable, authors found criteria suggested by Dawson IP et al., most reproducible for diagnosis of extranodal lymphoma. As per Dawson criteria, lymphoma is said to be primarily extranodal if there is: 1) absence of palpable superficial lymph nodes on first physical examination; 2) absence of mediastinal lymphadenopathy detected on plain chest X-ray; 3) dominant lesion at extranodal sites; 4) involvement of lymph nodes in the vicinity of the primary lesion; and 5) White Blood Cell (WBC) count within normal range [4]. All cases which qualified according to the Dawson criteria were included and cases which did not fulfill criteria were excluded.

All the cases were reviewed by minimum of two pathologists and were classified upon morphologic and immunophenotyping criteria according to World Health Organisation (WHO) 2008 classification [16]. Tumours were classified into B-cell lymphoma, T-cell lymphoma and NHL (unclassifiable). Cases for which IHC was inconclusive were classified as NHL (unclassifiable). B-cell and T-cell lymphoma were further subclassified.

STATISTICAL ANALYSIS

All statistical analysis was done by Statistical Package for Social Sciences (SPSS) software. The values were represented in number, percentage (%), mean and ratio.

RESULTS

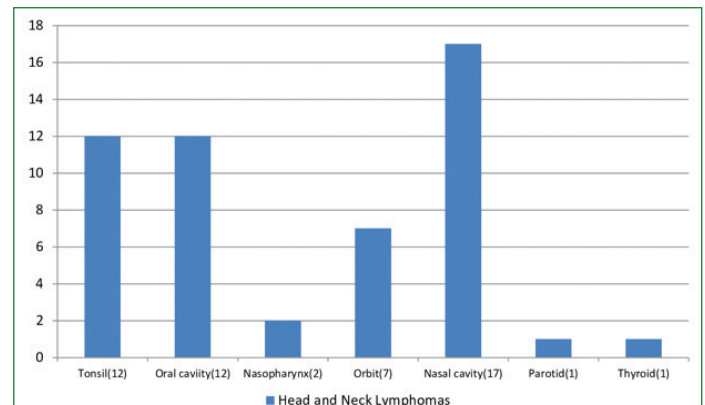
Total of 362 cases of NHL were reported. Out of which, 130 (36%) cases were of extranodal NHL which were studied. Total 90 cases were males and 40 cases were females with male to female ratio being 2.25:1. Mean age of presentation was 38.5 years. Paediatric cases constituted 32/130 cases (24.6%). Head and neck constituted the most common site (52/130; 40%) followed by GIT (21/130; 16.2%) and central nervous system (13/130; 10%), thorax (10/130; 7.7%), intra-abdominal (9/130; 6.9%), skin (6/130; 4.6%), soft tissue (6/130; 4.6%). The different sites that were involved by primary extranodal lymphoma are enumerated in [Table/Fig-1].

Site	Frequency (n=130)	Percentage (%)
Head and neck	52	40
Gastrointestinal tract	21	16.2
Central nervous system	13	10
Thorax	10	7.7
Intra-abdominal	9	6.9
Skin	6	4.6
Soft tissue	6	4.6
Bone	6	4.6
Hepatobiliary	4	3.1
Breast	1	0.8
Uterus	1	0.8
Testis	1	0.8

[Table/Fig-1]: Site wise distribution of extranodal lymphoma.

The B-cell NHL constituted 81/130 (62.3%), T-cell NHL 20/130 (15.4%) and NHL (unclassified) were 29/130 (22.3%). Amongst B-cell type NHL, DLBCL was the most common subtype (70/81; 86.4%) followed by B-cell NHL unclassifiable (U) (5/81; 6.2%), extranodal marginal zone lymphoma of Mucosa Associated Lymphoid Tissue (MALT) type (2/81; 2.5%), follicular lymphoma (2/81; 2.5%) and Burkitt's Lymphoma (2/81; 2.5%).

Amongst the head and neck Extranodal Lymphoma (ENL), male to female ratio in head and neck lymphomas was 3:1 and paediatric cases were 9/52 (17.3%). Nasal cavity (17/52; 32.7%) was the most common site followed by tonsil (12/52; 23.1%), oral cavity (12/52; 23.1%), orbit (7/52; 13.5%). Thyroid (1/52; 1.9%) and parotid (1/52; 1.9%) were rare sites [Table/Fig-2]. The DLBCL was the most common subtype amongst the head and neck category. The NK/T cell subtype accounts for majority of lymphomas in nasal cavity (8/17; 47.1%).

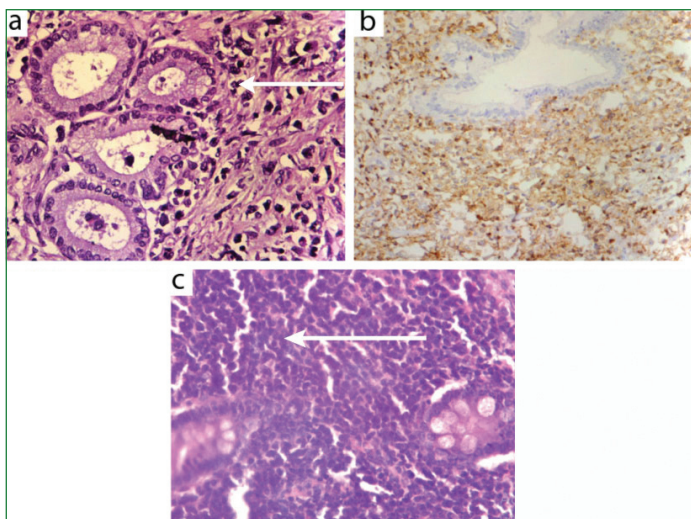


[Table/Fig-2]: Sites of involvement in head and neck lymphomas.

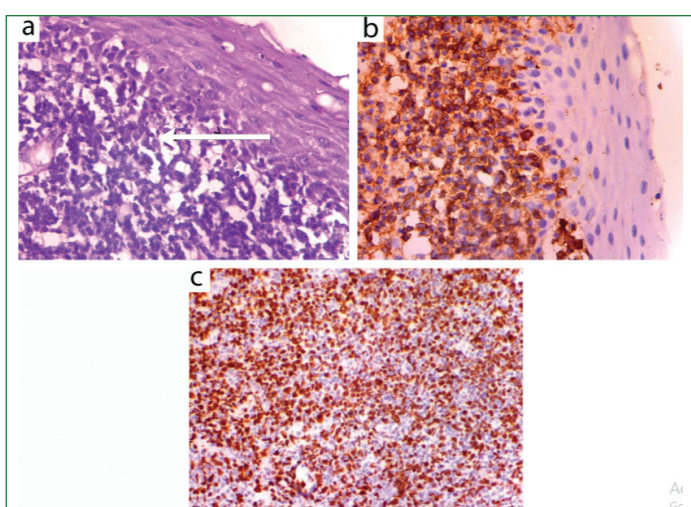
Amongst GIT lymphomas, male to female ratio was 3:1, paediatric cases accounted for 8/21 (38.1%). Common sites among the GIT lymphomas were stomach (6/21; 28.6%), small intestine (10/21; 47.6%) and large intestine (5/21; 23.8%). DLBCL was the most common subtype (8/21; 38.1%) followed by MALToma (2/21; 9.5%) and Burkitt's lymphoma (2/21; 9.5%). Both cases of Burkitt's lymphoma were of paediatric age group.

Male to female ratio in CNS lymphoma was 1.4:1. Paediatric cases accounting for 3/13 cases (23.1%). DLBCL was most common subtype reported (6/13; 46.2%). Taking into account the paediatric cases of extranodal lymphoma, head and neck (11/32; 34.4%) was most common site, followed by GIT (8/32; 25%). Within paediatric lymphomas, burkitt's lymphoma was most common (24/32; 75%) followed by lymphoblastic lymphoma (6/32; 18.8%) and two cases of DLBCL (2/32; 6.3%).

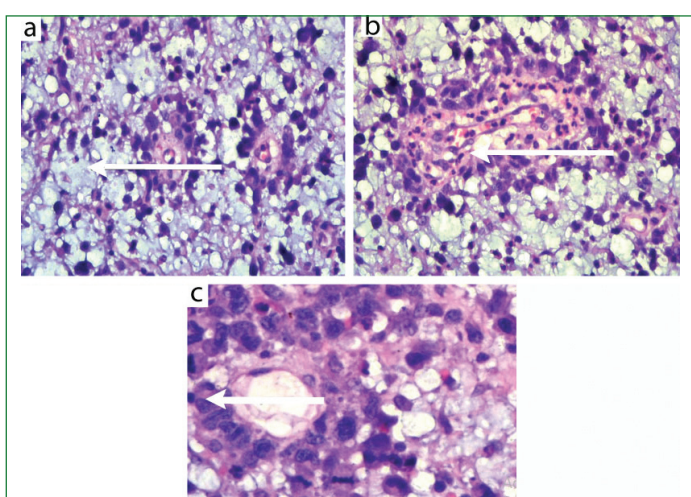
Present study also included few interesting cases which became diagnostic dilemma because of rarity of subtypes at particular site. Rare cases in the present study included primary DLBCL of gall bladder [Table/Fig-3], tongue [Table/Fig-4], uterus and breast. There was one case of cutaneous lymphomas in axillary region which turned out to be a rare case of myxoid variant of Anaplastic Lymphoma Kinase (ALK), negative Anaplastic Large Cell Lymphoma (ALCL). On light microscopy, sections from the case showed sheets of pleomorphic population of large polygonal to round cells having hyperchromatic nuclei and abundant eosinophilic cytoplasm. These neoplastic cells were at places were arranged in perivascular pattern. Distinctive myxoid change was seen throughout the tumour. Eosinophils, neutrophils, small lymphocytes and histiocytes were intimately admixed with the cells throughout the lesion [Table/Fig-5]. Detailed work up by IHC was done as the case was mimicking on histopathology as metastatic carcinoma. The neoplastic cells were negative for cytokeratin, melan A, desmin, myogenin, CD68, S100, EMA and CD34 with positivity for vimentin and LCA only. Retrospective examination of the tumour showed cells, having horse shoe (hallmark cells) and wreath-like nuclei along with few binucleated cells. The second panel of IHC showed that the neoplastic cells were strongly positive for CD30. The cells were negative for CD3, CD5, CD20, CD15, CD56 and ALK-1. The final diagnosis of primary cutaneous ALK negative T-cell ALCL, myxoid variant was made [Table/Fig-6].



[Table/Fig-3]: a) Case of diffuse large B-cell lymphoma of gall bladder. Atypical lymphoid cells (arrow) infiltrating the lamina (arrow) (H&E 400X); b) The above case is positive for immunohistochemistry Lymphocyte Common Antigen (LCA) (IHC 200X); c) Photomicrograph of case of Enteropathy associated T cell lymphoma of colon; Atypical lymphoid cells (arrow) infiltrating the lamina (H&E 200X).

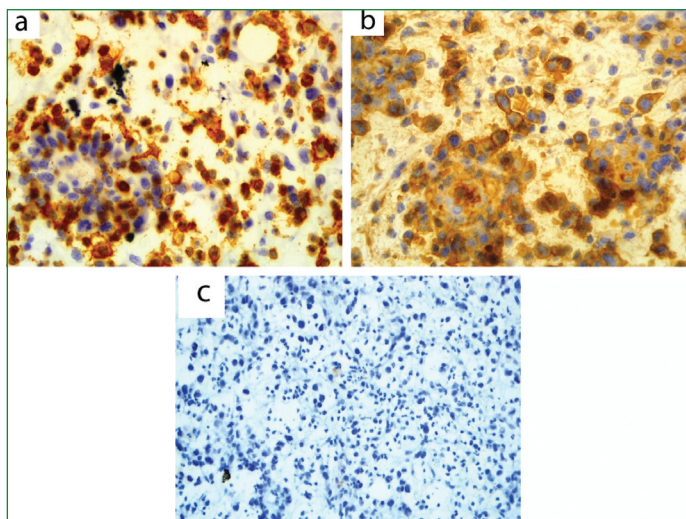


[Table/Fig-4]: a) Photomicrograph of case of diffuse large B cell lymphoma of tongue. Atypical lymphoid cells infiltrating submucosal zone (arrow) (H&E 200X); b) Atypical lymphoid cells are CD positive (IHC 200X); c) Atypical lymphoid cells have KI-67 (IHC 200X).



[Table/Fig-5]: a) Photomicrograph of case of myxoid variant of ALK negative ALCL shows tumour cells present in myxoid background (arrow) (H&E 400X); b) Atypical lymphoid cells arranged around blood vessel (H&E 400X); c) Tumour cells displayed horse shoe-shaped nuclei in same case (arrow).

Amongst the CNS lymphomas, one of the cases was clinically and radiologically mimicking supratentorial meningioma and on histopathology it turned out to be DLBCL. Few interesting cases of primary bone lymphomas were reported. One case was of B-lymphoblastic lymphoma of a three year old female with lesion



[Table/Fig-6]: a) Atypical lymphoid cells are LCA positive in positive in case of myxoid variant of ALK negative ALCL (H&E 200X); b) Atypical lymphoid cells are CD30 positive; c) Tumour cells are ALK negative.

in distal femur. Amongst head and neck lymphomas, a case of follicular lymphoma was reported in a 13-year-old female in parotid. The IHC proved to be useful in making a diagnosis.

DISCUSSION

Extranodal NHL are a heterogeneous group of disorders with varying frequency in different parts of the world because of variations in epidemiology, geographical, ethnic, anatomic, aetiologic and morphological diversities.

Western literature suggests that the reported occurrence of extranodal NHL is 24-48% whereas Asian studies, including studies from India, shows incidence of 44% [2,3,5,7,17]. Another study from South India reports incidence of 36% (41/114) during four years study period [15]. Although some other studies from India show a lower incidence of 22% (68/308) and 22.6% (68/300) [13,14]. The incidence of pENL has been shown to be very high in neighbouring Kuwait (45%), China (44.9%-61.4%), Northern Iraq (48.3%), Pakistan (42%), Taiwan (47.2%), Japan (46.6%), Korea (55%) and Thailand (58.7%) [8,11,12,18-21]. Present study had incidence of 36%.

All these studies suggest that there are reasons for varying incidence in different population mentioned above, diverse definition criteria can be the cause of variation of incidence and also above studies are hospital based studies therefore are not true representative of population. A region wise cancer registry of ENL would address to above problem. A comparison between the present series with published series in regard to incidence, common and uncommon anatomical site and histopathological subtypes of ENL has been summarised in [Table/Fig-7] [7,11-14,18,20-22].

The GIT is the predominant site of extranodal lymphomas and the incidence is increasing throughout the world [10,12,15,18,20]. Although, head and neck region including Waldeyer's ring, nose and paranasal sinuses have been reported to be the most common sites of origin of pENL in various studies from different parts of China, India, Taiwan and Iraq [7,11,12,19]. Head and neck region (40%; 52/130) was most common site of involvement in present study which is in accordance with one of the studies from North India by Singh D et al., (50.9%) and also by Mishra P et al., (37%) [7,14]. Amongst the head and neck lymphomas nasal cavity, oral cavity and tonsil were most common sites of involvement in the present study.

The pattern of involvement of GIT lymphomas in present series was similar to findings of studies from India and also from western population [2,10,13]. Stomach was the most common site of involvement followed in frequency, by large intestine and small intestine. However, some studies from Kuwait and Iraq have reported higher incidence of localisation of ENL in intestine [8,12].

Author, year and place	Total number of NHL	Period	Number of pENL; n (%)	Common sites involved (%)	Uncommon sites	Histopathology
Pai A et al, [22] 2017, South India	114	4	41 (35.96)	GIT, Nasopharynx, testis	Long bones, maxillary sinus, skin and paraspinal soft tissue	DLBCL, B-cell NHL (U)
Mishra P et al., [14] 2015 Southern India	300	3	68 (22.6)	Head and Neck (37) GIT (29)	Breast, bone, thyroid, adrenal, ovary	DLBCL, PTCL, MALT
Padhi S et al, [13] 2012, Southern, India	308	5	68 (22)	Brain (29.5), GIT (25)	Bone, testes spleen, vulva, lacrimal gland, kidney	DLBCL, MALT
Singh D et al., [7] 2003, Northern India	241	3	106 (44)	Head and Neck (50.9), GIT (27.4)	Brain, skin, bone, testis, UB	DLBCL
Yang QP et al., [11] 2011, China	5549	9	2968 (53.5)	WR#, GIT, Nasopharynx, Skin	CNS, orbit, bone, thyroid, salivary gland, testes, breast	DLBCL, ENKTCL, MALT
Yaqo RT et al., [12] 2011, Iraq	205	7	99 (48.3)	Intestine, WR, Nose, Stomach skin	CNS, orbit, bone, thyroid, salivary gland, testes, breast	DLBCL, BL, MALT
Yoon SO et al., [21] 2010, Korea	48	11	48 (100)	-	Adrenal, ovary esophagus, prostate pancreas, uterus	DLBCL (MC)
Fujita A et al., [20] 2009, Japan	847	7	395 (46.6)	GIT, WR, Orbit	Bone, thyroid, skin, prostate, testis, CNS, breast, uterus	DLBCL, MALT
Lal A et al., [18] 2008, Pakistan	557	16	235 (42)	GIT, Aerodigestive	Bone, breast, testis, CNS, skin	ENL at early stage, favorable
Present study, 2018, Northern India	362	4	130(36)	Head and Neck, GIT	Breast, testis, uterus	DLBCL

[Table/Fig-7]: Comparison between present and other studies in relation to Incidence, anatomic, histopathologic subtype.

*Gastrointestinal tract; †Waldeyer's Ring; PTCL: Peripheral T-cell lymphomas; MALT: Mucosa-associated lymphoid tissue; ENL: Erythema nodosum leprosum

Primary central nervous system lymphomas account for less than 2% of ENL but the incidence is increasing in immunocompromised and immunodeficient host [20]. In our series the incidence was higher and accounted for 10% of ENL. The DLBCL is the most common histopathologic subtype reported in literature in ENL followed by marginal zone lymphomas of MALT type. In present study, DLBCL contributing to most of the cases followed by B-NHL (unclassified) and extranodal marginal zone lymphoma. Mantle cell lymphoma cases were not reported in our series [23]. Interestingly, our study had a higher incidence of NK/T cell lymphomas (10%) as compared to other studies from Indian subcontinent [7,13]. Our findings were in concordance with another study from southern India by Mishra P et al., (26.5%) [14].

The patients of extranodal NHL were younger in comparison to other studies [13,14]. Most common site in paediatric ENL was large intestine and most common histopathologic subtype was Burkitts lymphoma followed by lymphoblastic lymphoma. These findings were in accordance with a study from Kuwait [8]. Few rare subtypes were highlights of present study. A case of primary cutaneous ALK negative ALCL was reported in a 50-year-old male in axillary region. The case was a diagnostic dilemma as it had extensive myxoid change mimicking other tumours of similar histology. Large panel of IHC was applied and the diagnosis was made. The above case emphasises the role of IHC in making diagnosis of rare variety of ENL at rare sites. Primary ALCL accounts for approximately 9% of all cutaneous T-cell lymphomas. ALK expression is common in systemic ALCL and rare in Primary Cutaneous Anaplastic Large Cell Lymphoma; its expression in skin is a warning to look for systemic disease [24].

The IHC plays a very important role in making a diagnosis and subtyping of extranodal lymphomas. Various common tumours come in differential diagnosis as far as site of extranodal and considering age of patient. Considering head and neck lymphomas carcinomas need to be ruled out, hence a primary panel including pan cytokeratin needs to be applied. At intra-abdominal sites in paediatric age group all the tumours which come under the category of small blue round cell tumours needs to be ruled out. This category includes rhabdomyosarcoma, extra skeletal Ewing's/PNET and Desmoplastic small round cell tumour. Hence, the IHC panel which authors used for excluding these morphological differentials were desmin and myogenin to rule out rhabdomyosarcoma, CD99 and FLI-1 to rule out Ewing's/PNET. Similarly, Embryonal tumours come

in close differential diagnosis of CNS lymphomas. At rare sites like soft tissue, monophasic synovial sarcomas come in close differential of primary lymphomas. One of our patients presented with ALCL at subcutaneous site at back which is a rare site of presentation. This patient became a diagnostic dilemma and after applying sarcoma and carcinoma panel, lymphoma was added in the panel in IHC [25]. Therefore, above cases very well described the confusing presentation of extranodal Lymphomas and judicious use of IHC interestingly solves the problem.

Present study included a case of DLBL of vagina. Incidence of extranodal lymphomas of female genital tract ranges from 0.5-1.5% [26,27]. In present series, one case of DLBCL of salivary gland was reported. Primary lymphomas arising in the salivary glands are uncommon with an incidence of 1.5 to 5% of all salivary gland neoplasms [28,29]. Primary gall bladder lymphomas are extremely rare with only case reports and case series reported [30]. Present study had one case of gall bladder DLBCL.

Limitation(s)

Present study also has some limitations. As it is a retrospective study, only epidemiological and morphological data were included and clinical follow-up of patients could not be obtained. Further, in depth studies and regional cancer registry is required for better understanding of epidemiology of these tumours.

CONCLUSION(S)

To conclude, incidence in India is lower as compared to data from other parts of the world. Patients in the present study were younger. Head and neck was most common site of involvement. The GIT lymphoma had a similar pattern of involvement of anatomic sites as data from other parts of world. The IHC plays a very important role in cases of diagnostic dilemma.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Nov 15, 2021
- Manual Googling: Nov 29, 2021
- iThenticate Software: Dec 14, 2021 (16%)

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- Financial or Other Competing Interests: None
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- Was informed consent obtained from the subjects involved in the study? No
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