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Original Article

Pathology Section

Primary Extranodal Lymphomas: A Five Year Retrospective Study from a Tertiary Care Cancer Centre, Kerala, India

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ABSTRACT

Introduction: Primary Extranodal Lymphomas (pENLs) are defined as lymphomas with dominant extranodal involvement with no or minor involvement of lymph nodes after routine staging procedures. The present study highlights the profile of pENLs in Kerala, South India which is not yet reported in literature.

Aim: To study the frequency, distribution and histopathology profile of pENLs diagnosed in a tertiary care cancer centre.

Materials and Methods: This was a retrospective cross-sectional study done in a tertiary care cancer centre in Kerala, Southern India for a period of five years. All the cases of pENLs diagnosed during this five year period which fulfilled the inclusion criteria were included in this study. These 3,357 cases were reviewed and classified according to the 2017 revised 4th edition World Health Organisation (WHO) classification of Tumours of Haematopoietic and Lymphoid tissues. Data was summarised using descriptive statistics. The frequency, distribution and histopathology features of pENLs were studied.

Results: A total number of 3,357 lymphomas were diagnosed at the centre during this period. Non Hodgkin lymphomas (NHLs) constituted of 2610 (77.7%) cases. pENLs constituted 477 cases which included two cases of classical hodgkin lymphomas. Primary extranodal NHL (n=475) constituted 18.2% of NHL. Diffuse large B-cell lymphoma (DLBCL), Not Otherwise Specified (NOS), was the most common histologic subtype (173 cases, 36.2%) followed by Mucosa Associated Lymphoid Tissue (MALT) lymphoma (77cases, 16.1%). Most common site of presentation were Gastrointestinal Tract (GIT) (117 cases, 24.5%) and Head and Neck region (HN) (117 cases, 24.5%).

Conclusion: DLBCL, NOS was the most common subtype. GIT and HN region was the most common site of pENLs in present study. The frequency of pENLs in present study was comparable to few other Indian studies but was lower than Far Eastern studies. The frequency of Adult T-cell leukaemia/Lymphoma (ATLL) was high which was not mentioned in similar studies on pENLs from India.

Keywords: Diffuse large B-cell lymphoma, Distribution, Frequency, Gastrointestinal tract, Head and neck, Histopathology

INTRODUCTION

Extranodal lymphomas as an entity was described in an extensive review by Dr. Saul Rosenberg in 1961 [1]. The designation of extranodal lymphomas is controversial especially in the presence of nodal and extranodal disease. The first definition was proposed by Dawson for primary gastric lymphomas [2]. Primary gastric lymphomas was defined as lymphomas with dominant disease manifestation in the stomach with or without regional lymph node involvement. Later the criteria were modified to allow for contiguous involvement of other organs and distant nodal disease providing that the extranodal site was the presenting site and constituted the predominant disease bulk. The definition of extranodal lymphomas is complicated by the designation of extranodal vs extralymphatic site as lymphomas of tonsils and waldeyer's ring, spleen, thymus can be considered as arising from lymphatic tissues and thus not considered as extranodal lymphomas.

But since most clinicians prefer nodal from extranodal disease rather than lymphatic from extralymphatic disease, the term extranodal lymphomas was gradually considered to indicate presentation outside lymph node [3]. There is great variability in the propotion of extranodal lymphomas due to variable reporting criteria, diverse definition of extranodal lymphomas, data sources from referral cancer centres and population based registries and the geographic difference due to the prevalence of Ebstein Barr virus and Human T-cell lymphotropic virus-1 infection. The present study aimed to determine the frequency, distribution and histopathology profile of pENLs diagnosed in a tertiary care cancer centre in Kerala, Southern India.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted in a tertiary care cancer centre in Kerala, Southern India for a period of five years from 1st January 2013 to 31st December 2017. The analysis of the study was done from January 2020 to December 2020.

All the cases of pENLs diagnosed in the tertiary care cancer centre during the five year period which fulfilled the inclusion criteria were included in the study.

Inclusion criteria: In this study, cases classified as pENLs include patients with disease manifestation outside lymph nodes or lymphoid strutures like spleen, waldeyer's ring and thymus and in those the extranodal site constituted the presenting site and bulk of disease with no or minor lymph node involvement after routine staging procedures [4,5].

Exclusion criteria: Cases of pENLs with incomplete staging procedures or with minimal tumour tissue were excluded from the study.

Study Procedure

The fresh specimens were fixed in 10% neutral buffered formalin. Paraffin embedding was done and histopathology sections were cut from paraffin embedded tissue at a standard thickness of 4 µm and morphologic examination was done in Haematoxylin and Eosin (H&E) stained sections. Panel of antibodies were decided after morphologic evaluation and the cases were classified according to the revised 4th edition WHO classification of Tumours of Haematopoietic and Lymphoid tissues [6]. All the selected patients had routine staging procedures including whole body CT scan and

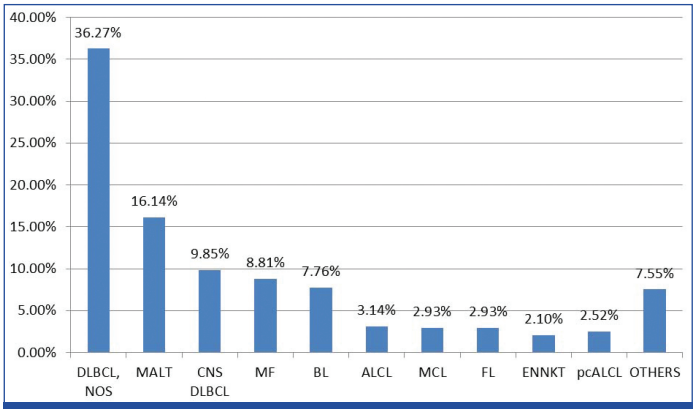
bone marrow studies. Frequency, distribution and histopathology features of pENLs were analysed and compared with various other similar studies.

STATISTICAL ANALYSIS

Data of pENLs were entered in Microsoft excel spreadsheet. Data was summarised using descriptive statistics. The categorical variables were reported using percentages.

RESULTS

A total number of 3,357 lymphomas were diagnosed at our Centre during this period. Non Hodgkin lymphomas (NHLs) constituted 2,610 (77.7%). pENLs constituted 477 cases which included two cases of classical hodgkin lymphoma. Primary extranodal NHLs constituted 475 (18.2%) of NHLs. Majority of the patients were males 310 (65%) and age ranged from 3-85 years. Majority of patients were adults 442 (92.7%). Frequency of histopathological subtypes of ENLs in this study is shown in [Table/Fig-1].

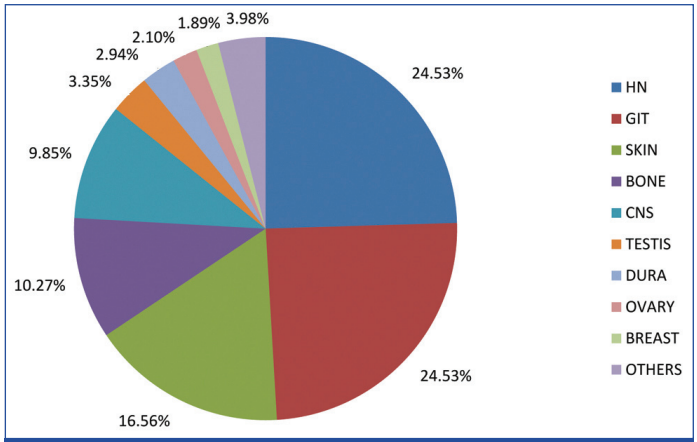


[Table/Fig-1]: Frequency of histopathological subtypes of ENLs. DLBCL, NOS: Diffuse large B- cell lymphoma, not otherwise specified: MALT: Mucosa-associated lymphoid tissue; CNSDLBCL: Primary DLBCL of CNS; MF:Mycosis fungoides; BL: Burkitt lymphoma; ALCL: Anaplastic large cell lymphoma; MCL:Mantle cell lymphoma; FL: Follicular lymphoma; ENNKT: Extranodal NK/T-cell lymphoma, nasal type; pcALCL: Primary cutaneous anaplastic large cell lymphoma

Diffuse large B-cell lymphoma, NOS (DLBCL, NOS) was the most common (173 cases, 36.2%) followed by MALT lymphoma (77 cases, 16.1%), Primary diffuse large B-cell lymphoma of the Central Nervous System (CNS) (CNS DLBCL) (47 cases, 9.8%), Mycosis fungoides (MF) (42 cases, 8.8%), Burkitt lymphoma (BL) (37 cases, 7.7%), Anaplastic Large Cell Lymphoma (ALCL) (15 cases, 3.1%) Mantle Cell Lymphoma (MCL) (14 cases, 2.9%), Follicular Lymphoma (FL) (14 cases, 2.9%), Primary cutaneous Anaplastic Large Cell Lymphoma (pcALCL) (12 cases), Extranodal NK/T-cell lymphoma, nasal type (ENNKT) (10 cases). Others include High Grade B-cell Lymphoma (HGBCL) (8 cases), Adult T-cell Leukaemia/ Lymphoma (ATLL) (7 cases), B-lymphoblastic lymphoma (B-LBL) (4 cases), Lymphomatoid papulosis (LyP) (4 cases), Lymphoplasmacytic lymphoma (LPL) (3 cases), Primary Diffuse large B-cell lymphoma, leg type (PCLBCL) (2 cases), Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (2 cases), Plasmablastic lymphoma (PBL) (2 cases) Classical hodgkin lymphoma (CHL) (2 cases), Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (1 case), Primary Cutaneous Gamma delta T-cell Lymphoma (PCGD-TCL) (1 case).

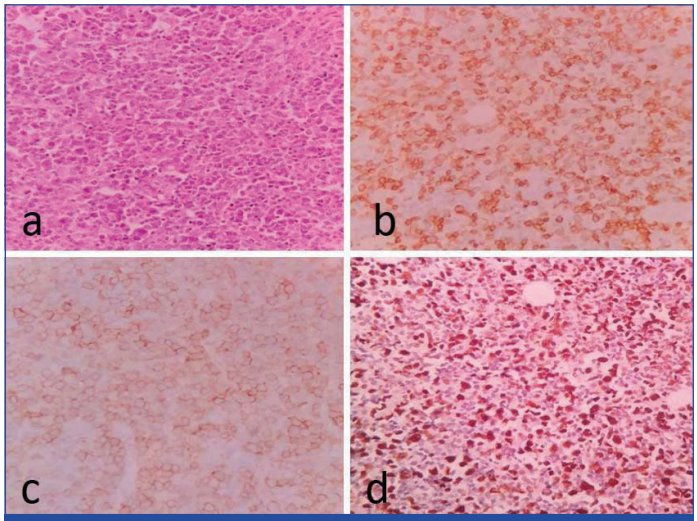
Most common site of presentation were gastrointestinal tract (GIT) (117cases, 24.5%) and head and neck region including orbit, nasal cavity and thyroid (117 cases, 24.5%) followed by skin (79 cases, 16.5%), bone (49 cases, 10.2%) central nervous system (CNS) (47 cases, 9.8%), testis (16 cases, 3.3%), epidural (14 cases, 2.9%), ovary (10 cases), breast (9 cases), lung (8 cases), kidney (4 cases), soft tissue, bone marrow (BM) (3 cases each), prostate (1 case) [Table/Fig-2].

Extranodal site in the two cases of classical hodgkin lymphoma were rectum and bone respectively. Bone marrow involvement was



[Table/Fig-2]: Sites of ENLs.

present in nine cases including four cases of BL, three cases of LPL primarily involving the bone marrow, one case of Extranodal NK/T-cell lymphoma (ENNKT) and one case of MCL. A single case of cutaneous ATLL showed peripheral blood involvement without bone marrow involvement. Few interesting cases were included in this study like B-lymphoblastic lymphoma involving kidney, extranodal NK/T-cell lymphoma involving the GIT without involving nasal cavity, extranodal NK/T-cell lymphoma with bone marrow involvement and plasmablastic lymphoma co-expressing CD3 with primary cutaneous presentation which was mistaken as peripheral T-cell lymphoma from outside centre. [Table/Fig-3] shows histopathology of extranodal NK/T-cell lymphoma, nasal type composed of medium to large tumour cells arranged diffusely. Tumour cells are CD3 positive, CD56 positive, negative for other B- cell, T-cell and plasma cell markers by immunohistochemistry and positive for EBV-encoded small RNA (EBER) by In-situ Hybridisation (ISH). [Table/Fig-4] shows plasmablastic lymphoma involving skin. Tumour cells were positive for CD138, MUM1, CD3, negative for other T- cell and B- cell markers by immunohistochemistry and positive for EBER by in-situ hybridisation.

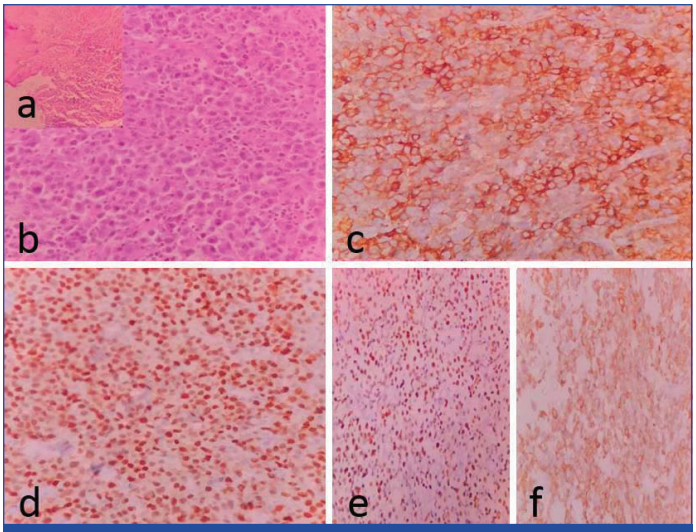


[Table/Fig-3]: a) Atypical medium to large cells are arranged diffusely (H&E, x400); b) Tumour cells are CD3 positive (IHC, x400); c) CD56 positive (IHC, x400); d) EBER-ISH positive (ISH x400).

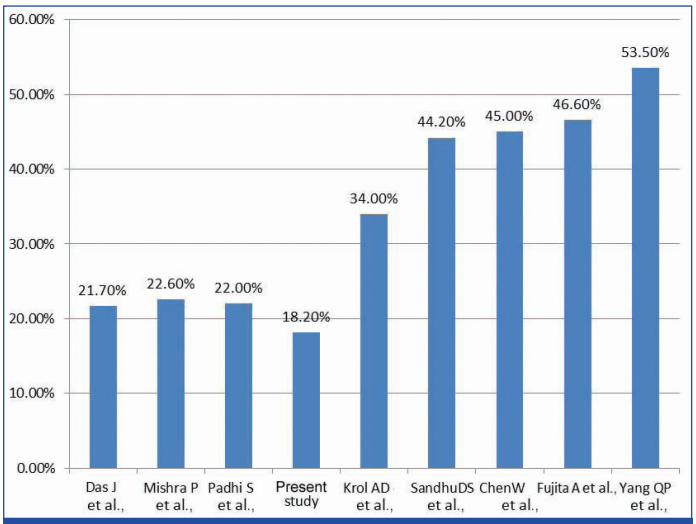
DISCUSSION

ENLs accounted for 18.2% of NHLs in this study which is comparable to previous three Indian studies but is significantly less than far Eastern studies [Table/Fig-5] [7-14].

Extranodal lymphomas constitute around 24-48% of non hodgkin lymphomas in Western studies [3,14-16]. Far eastern studies had the higher frequency of extranodal lymphomas possibly due to higher incidence of Ebstein-Barr virus and Human T-cell lymphotropic virus-1 infection. Frequencies of histopathological subtypes of pENLs as compared to other Indian, Western and Far Eastern studies are

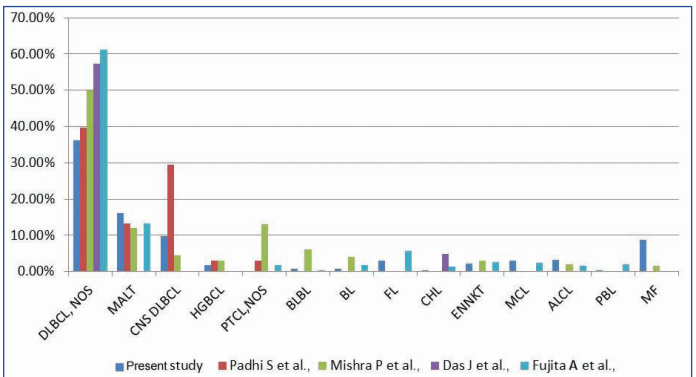


[Table/Fig-4]: a) Shows skin with underlying infiltrate of atypical cells. (H&E, x40); b) Large atypical cells with prominent nucleoli. (H&E, x400); c) Tumour cells are CD138 positive (IHC, x400); d) Tumour cells are MUM1 positive (IHC, x400); e) EBER-ISH positive (ISH x400) f) CD3 positive (IHC, x400).



[Table/Fig-5]: Frequencies of ENLs in our study as compared to other geographic regions [7-14].

shown in [Table/Fig-6] [7-9,13]. DLBCL, NOS was the most common subtype constituting around 36.2% followed by MALT lymphoma which is similar to another Indian study by Padhi S et al., [7] DLBCL was the most common histologic subtype in all the studies.



[Table/Fig-6]: Comparison of subtypes of ENLs in our study and other studies [7-9,13].

The frequency of MALT lymphoma was similar to other Indian studies. There are two cases of primary extranodal classical hodgkin lymphoma in our study as compared to three cases in another Indian study by Das J et al., [9]. The frequency of burkitt lymphoma, ALCL, ENNKT, PBL was comparable to study by Mishra P et al., [8]. High frequency of ENNKT is reported from China due to endemic nature of EBV infection [11]. Two cases of ENNKT were unusual in that one case presented with bone marrow involvement and the other case presented with intestinal involvement with differential of EATL which was confirmed by EBER-ISH [Table/Fig-3]. ENNKT can rarely arise in GIT. Most commonly involved site is intestine. Histopathology and immunohistochemistry findings often overlap with EATL. In ENNKT, CD56 is commonly expressed and show positivity for EBER [17]. B-LBL comprised four cases of ENLs in this study. Bone was the primary site of B-LBL in two cases while ovary and kidney are the primary sites in the other two cases respectively. There are only case reports of B-LBL involving kidney [18]. This was a 32-year-old female who presented with renal mass. Nephrectomy was done and diagnosed from outside centre as primitive neurectodermal tumour. Mishra P et al., reported three cases of B-LBL [8]. Primary site of two cases of PBL were skin and stomach respectively. Primary cutaneous PBL occured in an immunocompetant patient and tumour cells showed co-expression of CD3. Tumour cells were negative for other T-cell and NK-cell markers [Table/Fig-4]. Such cases can be easily mistaken as PTCLs as occurred in this case, if only a limited antibody panel is used in immunohistochemistry [19]. ATLL is a T-cell lymphoma caused by Human T-cell Laeukemia Virus type-1 (HTLV-1). Cases suggestive of ATLL were confirmed by serum HTLV-1 assay. ATLL accounted for around 8.40% of PTCLs in a study from Kerala [20]. Another study had reported 15 cases of HTLV-1 positive ATLL from Kerala which is the second largest study series from Asia after Japan [21]. MF accounted for around 8.81% which was comparable to study by Padhi S et al., [7]. There was a single case of EATL involving ovary. Gastrointestinal tract and head and neck region constituted the most common site. Head and neck constituted the most common site in studies by Mishra P et al., and Sandhu DS et al., [8,10]. Padhi S et al., reported CNS as the most common site of pENLs [7]. GIT was the most common site in the study by Fujita A et al., [13] Few entities like lymphomatoid papulosis, Primary cutaneous Anaplastic Large Cell Lymphoma (pcALCL), Adult T-cell leukaemia/Lymphoma (ATLL), lymphoplasmacytic lymphoma, primary cutaneous follicle centre lymphoma, primary Diffuse large B-cell lymphoma, leg type, subcutaneous panniculitis-like T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, primary cutaneous gamma delta T-cell lymphoma, sezary syndrome are not mentioned in other studies on ENLs from India.

Limitation(s)

The main limitations were treatment, follow-up and molecular studies of these cases were not done in present study.

CONCLUSION(S)

The frequency of pENLs were significantly lower when compared to Far Eastern studies. The frequency of ATLL was high which was not mentioned in studies on pENLs from other parts of India.

Larger studies incorporating treatment details, follow-up and molecular studies will help to better understand the pathogenesis and clinical outcome in pENLs.

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