

Leukemia - Lymphoma and Myeloma

# Primary Extranodal Non-Hodgkin Lymphomas: A First Tertiary Care Experience from Punjab, North India

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## Abstract



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## Keywords

- ▶ extranodal
- ▶ India
- ▶ lymphomas

**Background** Primary extranodal lymphomas are less frequently encountered and difficult to diagnose in routine practice. The histopathological and immunohistochemical studies are essential in addition to clinical details to diagnose. The incidence is varied in different parts of India along with variation in histopathological spectrum.

**Methodology** The clinical features and histopathological findings of patients diagnosed with primary extranodal lymphoma over 3-year period were retrieved from archives of pathology department and analyzed.

**Results** During the 3-year study period, a total of 135 cases of non-Hodgkin lymphomas were evaluated, and of these, 41.4% (56/135) of cases presented with primary extranodal involvement. The mean age of primary extranodal lymphoma presentation was  $61.3 \pm 17.5$  with M:F ratio of 1:1.1 Most common extranodal site involved was gastrointestinal tract 32.1%, 18/56 (small intestine [17.8%, 10 cases] and large intestine [8.9%, 5 cases]). Non-Hodgkin lymphomas of B cell type were the predominant subtype (48/56, 85.7%), while 8/56 (14.2%) cases were of T cell lineage. Of the B cell non-Hodgkin lymphoma diffuse, large B cell lymphoma was the predominant subtype constituting ~83.3% (40/48).

**Conclusion** Primary extranodal lymphomas exhibit varied histomorphological and clinical presentation. The present study is first such analysis from Punjab that intends to compare with studies from other parts of India.

## Introduction

Primary extranodal lymphoma (pENL) constitutes ~25% of all non-Hodgkin lymphoma (NHL) and refers to group of disorders arising from tissues other than lymph nodes. pENL is a frequent diagnostic challenge to the clinicians and pathologists due to their varied clinical presentations, histomorphological mimicry, and molecular alterations. The incidence of pENL is increasing and is attributed primarily

to improved knowledge in diagnostic immunophenotyping and imaging modalities. The common sites involved include the central nervous system, the gastrointestinal tract (GIT), and the skin.<sup>1-3</sup> This site-specific incidence might be attributed to environmental factors, chronic infections, immunosuppressive, and autoimmune disorders. Although there are many case reports and series dealing with extranodal lymphoma of the various sites of the body, the literature from North India, especially Punjab on pENL, is limited.

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## Methodology

### Study Design

The present 3-year retrospective study was conducted in the Department of Pathology, Dayanand Medical College and Hospital, Ludhiana, Punjab. The demographic and clinical features, laboratory parameters, imaging findings, histopathology, and immunophenotyping of all the patients presenting with pENL were documented, and descriptive analysis was done.

### Case Selection

All patients who present with NHL that apparently originated at an extranodal site, even in the presence of disseminated disease, as long as the extranodal component, was clinically dominant were defined as extranodal lymphomas. Patients presenting with symptoms of lymphadenopathy and other systemic organ involvement were examined. Biopsy and excision specimens were fixed in formalin (10% solution of formaldehyde in buffered alcohol) and then processed and stained with hematoxylin and eosin stain. Immunohistochemistry was done in all cases for further typing and classification.

The study was approved by the institutional ethic committee (vide letter number BFUHS/2K17p-TH/11162), and appropriate consent of patients were taken.

## Results

During the 3-year study period, a total of 135 cases of NHL were evaluated, and of these, 41.4% (56/135) of cases presented with primary extranodal involvement. The mean age of pENL presentation was  $61.3 \pm 17.5$  with M:F ratio of 1:1.1. Organomegaly and B symptoms were noted in 28.5% (16/56) patients. Most common extranodal site involved was GIT 32.1%, 18/56 (small intestine [17.8%, 10 cases], large intestine [8.9%, 5 cases], and stomach [5.3%, 3 cases]) followed by thyroid (10.7%, 6 cases), brain (8.9%, 5 cases), liver (8.9%, 5 cases), spleen (5.3%, 3 cases), breast (3.5%, 2 cases), lung (3.5%, 2 cases), pancreas (3.5%, 2 cases), parotid (3.5%, 2 cases), tonsils (3.5%, 2 cases), and a single case (1.8%) each involving the followings sites such as chest wall, frontal sinus, kidney, bone, nasopharyngeal mass, rectal biopsy, scapula, skin, stomach, temporozygomatic mass, and testis.

NHL of B cell type were the predominant subtype (48/56, 85.7%), while 8/56 (14.2%) cases were of T cell lineage. Of the B cell NHL diffuse, large B cell lymphoma was the predominant subtype constituting ~83.3% (40/48), followed by marginal zone lymphoma, follicular lymphoma, and Burkitt lymphoma each constituting ~4.16% (2 cases each), precursor B-lymphoblastic lymphoma and chronic lymphocytic leukemia/small lymphocytic leukemia each constituting 2.13% (1 case each). Of the T cell lymphomas, peripheral T cell lymphoma not otherwise specified (NOS) 50% (4 cases) and precursor T-lymphoblastic lymphomas 22.2% (2 cases) were recovered followed by anaplastic large-cell lymphoma and cutaneous T cell lymphoma 11.1% (1 case each) (→Table 1).

**Table 1** Histomorphological and immunophenotypic subtypes of primary extranodal lymphoma

Histomorphological and immunophenotypic subtypes	Site	Number of cases (N = 56), n (%)
Diffuse large B cell lymphoma	GI, breast, kidney, lung, testis, spleen	40 (71.4)
Marginal zone lymphoma	Parotid	2 (3.5)
Follicular lymphoma	Bone, chest wall	2 (3.5)
Burkitt lymphoma	Large intestine, small intestine	2 (3.5)
Precursor B-lymphoblastic lymphoma	Liver	1 (1.7)
Small lymphocytic lymphoma	Liver	1 (1.7)
Peripheral T cell lymphoma NOS	Small intestine, liver	4 (7.0)
Precursor T-lymphoblastic lymphoma	Thyroid, liver	2 (3.5)
Anaplastic large cell lymphoma	Small intestine	1 (1.7)
Cutaneous T cell lymphoma	Skin	1 (1.7)

Abbreviations: GI, gastrointestinal; NOS, not otherwise specified.

## Discussion

pENLs are a heterogeneous group of tumors because of its difference in epidemiology and etiology in different areas around the world. The present 3-year study is the first experience from Punjab, North India, focusing on pENL. The most common site involved was GIT (18/56, 32.1%), of which small intestine (10/18, 55.5%) was the frequently involved. Diffuse large B cell lymphoma was the most common histological subtype of all the B cell NHL (40/48, 83.3%) that were further subclassified into germinal center subtype (19/40, 47.5%) and nongerminal center subtype based on Hans Classifier (CD 10, BCL6, and MUM 1).<sup>4,5</sup> Gogia et al also reported diffuse large B-cell lymphoma being the most common subtype with extranodal involvement in 34.8% patients. Fifty patients had pENL with stomach and intestine being the most common site followed by central nervous system. The information regarding cell of origin (based of Hans algorithm) was available for 160 patients; 88 (55%) were germinal center B-cell like and 72 (45%) were activated B-cell.<sup>6</sup>

The literature from India shows varied incidence as studies from southern India showed that extranodal lymphomas constitute around 22.6% in contrast to 44% of occurrence in northern part and 54.7% in western part, 31.1% in Northeast India in contrast to our study 41.4%. These variations in frequency in different parts of the same country may be attributed to variation in genetic or ethnic factors, environmental factor as well as the diverse definition criteria. The GIT is the predominant site of extranodal NHL accounting for almost one-third

**Table 2** Comparison of various studies from India relating to primary extranodal lymphomas

Author and years	Region	Duration of study (y)	NHL	pENL (%)	Age	Site	Most common histological subtype
Singh et al, 2003 <sup>4</sup>	North India	3	241	106 (43.9)	–	Head and neck	DLBCL
Padhi et al, 2012 <sup>5</sup>	South India	5	308	68 (22.07)	Mean age 43 y	Brain	DLBCL
Aparna et al, 2015 <sup>9</sup>	South India	3	–	31	–	Head and neck	DLBCL
Mishra et al, 2015 <sup>2</sup>	South India	3	300	68 (22.6)	Peak incidence 4th and 5th decade	Head and neck	DLBCL
Mehta et al, 2016 <sup>8</sup>	North West India (Rajasthan)	2	128	70 (54.6)	Peak incidence 5th and 6th decade	GIT	DLBCL
Pai et al, 2017 <sup>1</sup>	South India	4	114	41 (35.9)	Mean age 54.2 y	GIT	DLBCL
Lopa et al, 2018 <sup>3</sup>	North East	4	257	80 (31.1)	Mean age 51.9 y	Head and neck	DLBCL
Present study 2019	North India (Punjab)	3	135	56 (41.4)	Mean age 61.3 y	GIT	DLBCL

Abbreviations: DLBCL, diffuse large B cell lymphoma, GIT, gastrointestinal tract, NHL, non-Hodgkin lymphomas; pENL, primary extranodal lymphomas.

of all primary extranodal NHL, but this incidence may vary in different areas. Within the GIT, primary gastric NHL is by far the most common, comprising 50 to 60% of all GIT-NHL, and therefore, considered the most common site of extranodal lymphoma involvement in Korea and India. Another study from south India also emphasized that 15 to 20% cases of NHL have GIT as their primary site, of which stomach is predominantly affected.<sup>7</sup> The present study is different as small intestine was the most common site involved; this may be attributed to high inflow of patients suffering from celiac disease and inflammatory bowel disease at our center that is one of the predisposing factors from intestinal lymphomas. One case of peripheral T-cell non-Hodgkin lymphoma NOS of small intestine had prior history of celiac disease.

Head and neck region including Waldeyers' ring has been reported to be the most common sites of origin (44%) of pENL study from northern India by Singh et al whereas a study conducted by Padhi et al from southern India showed extranodal lymphomas constituted 22% and the most common site is the central nervous system; the western India shows incidence of 28% and GIT is the most common site that is affected. Mishra et al<sup>2</sup> from South India showed incidence of 22.6% with head and neck being the most common site of pENL.<sup>4,5,8,9</sup> The present study constitutes 41.4%, and GIT is the most common site involved. The data clearly show high incidence of pENL in North India as compared with South India with higher incidence of head and neck origin in South India as compared with North India (→ **Table 2**). These histomorphological diversities of pENL across India are difficult to explain but can be attributed to ethnic, environmental and genetic factors.

## Conclusion

pNELs are common in North India with wide variation in site of involvement as compared with other parts of the country. The diagnosis of pENL is always difficult in the

absence of immunohistochemical studies and clinicoradiological information.

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### Conflicts of Interest

There are no conflicts of interest.

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