

## Spectrum of manifestation of Primary extra nodal lymphomas - A retrospective case series and review of the literature.

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### Abstract

**Objective:** To study spectrum of manifestation and histopathological correlation of primary extra nodal NHL. **Material and method:** 15 cases of primary extra nodal NHL were included in this retrospective study. Clinical details include Age, gender, presenting symptoms were collected. Histopathological examination was performed. Immunohistochemistry was done based on histopathological morphology. **Result:** Out of the 15 subjects included in this study, 11 were male and 4 were female. 7 subjects were in the 5<sup>th</sup> decade of their lives. DLBCL (8 case) was most frequent variant of PENL followed by Anaplastic large cell lymphomas (3 case), Angioimmunoblastic T cell lymphoma (2 case) and Marginal zone lymphoma (2 case). **Conclusion:** Frequency of ENL is gradually increasing and has a highly variable clinical presentation. The clinician and pathologist should be aware of uncommon presentations. High level of suspicion will allow for an early diagnosis of pENL, which would in turn be helpful in improving the prognosis by early initiation of appropriate treatment.

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### Introduction

Lymphomas represent a heterogeneous group of hematological neoplasms. They are divided into Non Hodgkin's Lymphoma (70-80%) and Hodgkin's Lymphoma (20-30%). Commonly, lymphomas arise in the lymph nodes. Origin of malignant lymphomatous cells from sites other than lymph node is termed as Extra nodal lymphoma (ENL). It can arise from any part of body. The most frequently involve system is gastrointestinal tract. Stomach is the commonest affected organ followed by Waldeyer's ring, lung, liver, spleen, bone and skin[1].

Non Hodgkin's lymphoma (NHL) is a lymphoproliferative malignant neoplasm having varied histomorphological and clinical characteristics. The most common type of NHL is diffuse large B cell lymphomas (40%). Extra nodal lymphoma comprises of various histological types and highly varied clinical presentation. Diagnosis is often difficult when the clinical and/or radiological features mimics epithelial tumor or infection, but needs to be diagnosed as treatment is specific.

This study attempts to describe spectrum of patients presenting with extra nodal lymphoma (ENL). It highlights the polymorphic clinical presentation and the role of pathologist in diagnosis, and ultimately the management of patients.

### Material and Method

This is a retrospective descriptive case series of fifteen patients of primary extra nodal lymphoma collected from the department of pathology. It includes all case of primary extra nodal lymphoma diagnosed on the basis of histopathology. For this we adopted the proposal by Krol *et al*, who used a liberal definition of primary extra

nodal NHL that includes all patients who present with NHL that apparently originated at an extra nodal site, even in the presence of disseminated disease, as long as the extra nodal component was clinically dominant[2,3]. Tonsils and Waldeyer's ring were excluded as there is a debate about these being nodal or extra nodal.

Their detailed clinical presentation and approach to diagnosis is mentioned in Table 1. The Histopathological features of these varied sites are very distinct. The tissue was processed routinely in 10% formalin and paraffin sections were stained with haematoxylin and eosin. Immunohistochemistry (IHC) was performed using a panel of antibodies depending on the histomorphology. All cases were classified based upon morphological and immunophenotypic criteria according to World Health Organization (WHO) 2008 classification[4].

### Results

Distinct male preponderance of the disease was present with 11 out of 15 subjects being male. Nearly half of the cases (7 subjects) presented in the 5<sup>th</sup> decade of life with 2 subjects each presenting in 3<sup>rd</sup>, 4<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> decades.

All the patients in this study had distinct clinical presentation (table1). Although four patients had abdominal symptoms, tumor origin in them was from small gut, undescended testis, lower abdominal soft tissue and anorectum. Two patients each presented with a breast lump, proptosis and non healing ulcer over the knee whereas one patient had a non healing ulcer over the toe. One patient each presented with a scapular region lump, nasopharyngeal mass, sub axillary mass, and dyspnoea due to lung mass.

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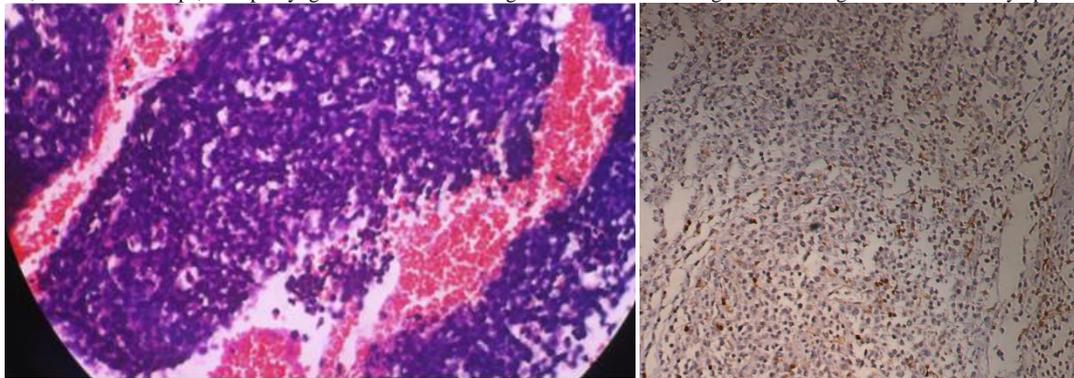
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**Table 1: Detailed description of the subjects included in this case series. ABR: SCC: Squamous cell carcinoma, NPC: Nasopharyngeal carcinoma, DLBCL: Diffuse large B cell Lymphoma, IHC Immunohistochemistry.**

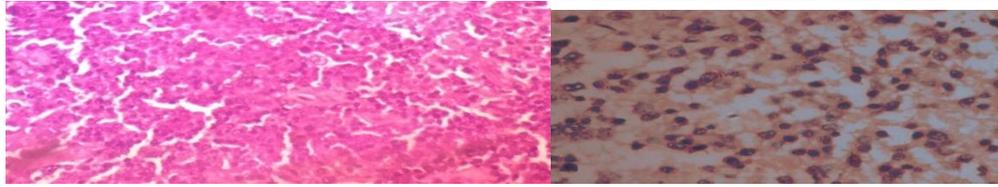
Serial number	Age	Sex	Clinical presentation	Clinical diagnosis	Histopathology	IHC	Final diagnosis
1	44	M	Soft tissue swelling measuring 12x9 cm below the right scapula	liposarcoma	Angioimmunoblastic lymphoma	CD3,CD4 ,CD10 +	Angioimmunoblastic lymphoma
2	26	M	Non healing ulcer knee	SCC	Anaplastic Large cell lymphoma	CD30+	Anaplastic large cell lymphoma
3	45	M	Abdominal pain ,wt loss for 5 month	Adenocarcinoma small gut	DLBCL	CD20+	DLBCL
4	42	M	Nasopharyngeal mass	NPC	DLBCL	CD20+	DLBCL
5	42	F	Dyspnea and weight loss for 8 month	SOL in Right lung measuring 3x2 cm	DLBCL	CD20+	DLBCL
6	32	M	Non healing ulcer toe for 8 month	SCC	Anaplastic large cell lymphoma	CD30+	Anaplastic large cell lymphoma
7	46	F	Lump in breast 4x4 cm since 2 month	Ductal carcinoma	DLBCL	CD20+	DLBCL
8	38	M	Lt undescended testis with abdominal pain since 1 months	Undescended testis	DLBCL	CD45, CD20: Positive Ki 67: 80%-90%	DLBCL
9	45	M	Proptosis for 1 yr	Proptosis	Marginal zone lymphoma		Marginal zone lymphoma
10	62	M	Soft tissue swelling below right axillae 8x4 cm	Lymphoma	Angioimmunoblastic T cell lymphoma	CD3,CD4 ,CD10	Angioimmunoblastic T cell lymphoma
11	42	M	Non healing ulcer knee	SCC	Anaplastic large cell lymphoma	CD30+	Anaplastic large cell lymphoma
12	55	F	Breast lump	Ductal carcinoma	DLBCL	CD20+	DLBCL
13	55	M	Proptosis for 8 month	Proptosis	Marginal zone lymphoma		Marginal zone lymphoma
14	64	F	Anorectal mass 4 month	Malignant Round cell tumor	DLBCL	CD20+	DLBCL
15	20	M	Lump and pain in lower abdomen for 2 month	Soft tissue tumor	DLBCL		DLBCL

All the tumors were diagnosed by histopathological examination and were further confirmed by appropriate immunohistochemistry markers (table 1). Eight subjects were diagnosed as Diffuse large B cell Lymphoma (DLBCL) which included the four abdominal presentations, two breast lumps, nasopharyngeal mass and the lung

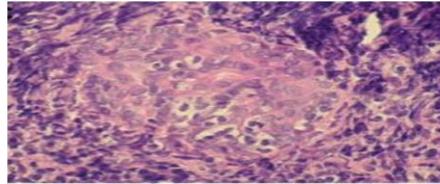
mass (Fig1). The three subjects with non healing ulcer over knees and toe were diagnosed as Anaplastic large cell lymphoma (Fig2). The two subjects with orbital presentation were diagnosed as Marginal zone lymphoma (Fig 3). The subjects with scapular and subaxillary masses were diagnosed as Angioimmunoblastic lymphoma (Fig4).



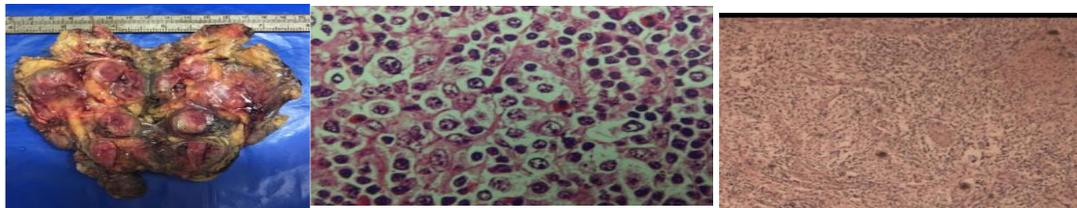
**Fig 1: Tumor composed of medium to large sized of cells with high NC ratio very scanty cytoplasm and prominent nucleoli admixed with large area of hemorrhage (400X).IHC shows CD20 positive.**



**Fig 2: Tumor comprising of sheets of pleomorphic large tumor cells with high NC ratio, and prominent nucleolus with few of the atypical cells having multiple nucleoli (400x) .CD30 positive tumor cell.**



**Fig 3: Histopathology of Marginal zone lymphoma shows well preserved reactive follicles with expanded marginal zone by monocytoid cells (400X)**



**Fig 4: Angioimmunoblastic T cell lymphoma presented as axillary swelling measuring 12X9 cm. Lymphoid follicles with a diffuse pattern of involvement and with numerous arborizing blood vessels lined by endothelial cells with high endothelial venules (400X).Tumor cell shows CD3 positive.**

#### Discussion

Non-Hodgkin's lymphoma (NHL) is the lymphoproliferative malignant neoplasms having varied histomorphological and clinical characteristics. The nodal type of NHL is the ones that arise from the lymphoid organs, while the lymphomas that arise from tissues other than the lymph node or the sites devoid of lymphoid tissue are the primary extra nodal type[4]. The extranodal lymphoma (ENL) is of two types - primary and secondary. The secondary ENL presents first in lymph nodes and involves the extra nodal sites subsequently[5]. The definition of primary EN-NHL is a controversial issue, especially in patients where both nodal and extra nodal sites are involved. The first definition of Extra Nodal Non Hodgkin Lymphomas (EN NHL) was given by Dawson for gastrointestinal lymphomas[6]. It was later refined by Lewin[7] and Herman[8]. On the other hand, studies that use more liberal criteria for EN-NHL include patients with disseminated disease[9, 10]. Studies from Western countries have reported the occurrence of extranodal NHL as 24-48% of all NHL[10, 11]. A study from Northern India by Singh *et al* showed extranodal lymphomas constitute 44% with the most common site being the head and neck[12]. Another study conducted by Padhi *et al* from southern India showed extra nodal lymphomas constituted 22% and the most common site being the central nervous system[13]. It is difficult to explain such diversities. Diffuse large B-cell lymphoma is the most common type of primary extranodal lymphoma. It is the most common type of lymphoma encountered in the gastrointestinal tract[13, 14]. Previously it was known to be a disease of older individuals, with a median age in the seventh decade, but frequency in younger adults and children are increasing. There is a slight male preponderance and this varies among anatomic sites. Diffuse large B-cell lymphoma most of time, presents with large, destructive lesions that may invade adjacent structures[15, 16]. Microscopic examination reveals a diffuse proliferation of large cells with round, oval, irregular bizarre or lobated nuclei, distinct nucleoli, and scant cytoplasm. In most cases, patients present with localized disease (Ann Arbor stage I or II)[13].

Diffuse large B-cell lymphoma almost always expresses pan-B-cell markers, such as CD20. Most express bcl-6, many are bcl-2, and a minority are CD10 positive. Rarely, they are CD5 63 positive; the differential diagnosis in such cases includes the blastoid variant of mantle cell lymphoma, but diffuse large B-cell lymphoma is negative for cyclin D1. Second most common type of pENL in our study was anaplastic large cell lymphoma. Anaplastic large cell lymphoma is an aggressive lymphoma of T cell lineage and was first described in 1985 as Ki-1 lymphoma, characterized by neoplastic proliferation of lymphoid cells which are anaplastic in appearance[17]. ALCL frequently involves the lymph nodes and rarely involves extra nodal site such as skin, soft tissue, liver, bone marrow, lungs, CNS[2, 10]. The site of origin as well as a fusion protein anaplastic lymphoma kinase (ALK) has been described as an important prognostic factor[18]. In our study all three cases presented as non healing ulcer of skin and were clinically diagnosed as squamous cell carcinoma. Two of the patients were in 5<sup>th</sup> decade of their lives whereas the third one was in 3<sup>rd</sup> decade. Primary cutaneous ALCL has a less aggressive disease course than the systemic type. Only 10 % of primary cutaneous ALCL extend beyond the skin to lymph node and are treated as systemic ALCL. It is characterized by tumor composed of large pleomorphic cells with prominent nucleoli and variable number of hallmark cell with horseshoe shaped nuclei[3, 19]. Also there is constant expression of the CD30 molecule on all neoplastic cells[20, 21]. Morphological similarity between ALCL and other lymphoma has been reported, and their growth in cohesive pattern mimics nonhematological malignancies like sarcoma, Germ cell tumors and melanoma[22, 23]. Third common type of extranodal lymphoma in our study was Angioimmunoblastic T cell lymphoma. Angioimmunoblastic T cell lymphoma cell lymphoma is a systemic disease often has evidence of extra nodal involvement. It is classified under T cell lymphoma and is considered to be a high grade lymphoma that affects T cells. It usually affect older people, typically around seventh decade and has varied clinical presentation. The two patients in this series are in fifth and seventh decade respectively. Common presentations

include lymphadenopathy, hemolytic anemia, skin rashes and rheumatoid arthritis. Rarely, it may present as skin ulceration and soft tissue masses as seen in the two cases in this case series. In our study both cases are presented as large soft tissue swelling near axillae and one patient is in 4<sup>th</sup> decade and other patients in his 6<sup>th</sup> decade and both are male. The classical histopathology is absence of follicles in lymph node with presence of high endothelial venules. Tumor cells are small to medium in size with pale cytoplasm. On IHC these cells are positive for CD3, CD4, CD10, BCL2 and CXCL13[24]. In our study we encounter two cases of extranodal Marginal B cell lymphoma. Both cases were male and presented with proptosis. Extranodal marginal zone B cell lymphoma is a low grade lymphoma that has been described in stomach and salivary gland. ENMZ lymphoma arises within acquired lymphoid tissue at a variety of extranodal sites. NHL of ocular adnexa constitutes less than 1% of all cases of nodal and extra nodal NHL[25]. MALT lymphoma of the ocular adnexa is characterized by an indolent natural history and by different biological and clinical features compared to MALT lymphomas of GIT. Histopathology shows well preserved reactive follicles with mantle zone and expanded marginal zone by monocytoid cells. Clinical and radiological correlation is must for diagnosis. The majority of pENL are of B-cell lineage with diffuse large cell type as the predominant type seen in approximately 50% of the cases of pENL. In our case series, we also have similar findings with DLBCL accounting for 7 out of 15 subjects (46.67%) of cases. The B-cell and T-cell lymphoma at the extra-nodal site have different clinical outcome than those at nodal site, thus requiring different treatment modalities and approach.

#### Conclusion

Primary extra nodal lymphomas constitute a diverse group of hematolymphoid malignancies whose prognosis depends upon the primary site and early diagnosis. The incidence of pENL is low in India compared to data from other parts of the world. These cases are discussed in order to sensitize the clinicians and pathologists with the varied presentation of primary extra nodal lymphomas. High level of suspicion will allow for an early diagnosis of pENL, which would in turn be helpful in improving the prognosis by early initiation of appropriate treatment.

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