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Primary extranodal lymphoma: unusual sites

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ABSTRACT

Background: Lymphoma arises in lymph nodes. Infiltration of malignant lymphomatous cells in the organs other than lymph node is termed as extranodal lymphoma (ENL). Almost any organ in the body can get affected. The most frequently involved system is gastrointestinal tract, followed by lung, liver, spleen, bone, and skin. Primary central nervous system (CNS) lymphoma is also well documented. Origin of tumor from non-lymph-nodal tissue is termed as primary ENL, whereas hematogenous spread of disease from lymph nodes to extranodal tissue is secondary ENL. Extranodal involvement is more common in non-Hodgkin's lymphoma (NHL) than Hodgkin's disease. **Aims and Objectives**: The aim of the study was to study the prevalence of primary ENLs at unusual sites. **Materials and Methods:** A prospective study was conducted for a period of 3 years to study the prevalence of primary ENLs at rare sites. **Results**: In our study, the participants were having a mean age of 50 years and showed a bimodal distribution. A total 16 cases were male (59%) and rest were female (11 cases, 41%). We found that B-symptoms were present in 19 cases (70%) and absent in the remaining. Most of the cases were of B- cell type (20 cases, 74%) and rest were T-cell type (seven cases, 26%). The most common extranodal site being gastrointestinal tract (10 cases, 37%) followed by CNS (four cases, 15%), spleen (two cases, 7%), tonsil (two cases, 7%), and cutaneous site (two cases, 7%). Other less common sites included breast, paranasal sinuses, mediastinum, floor of mouth, nasopharynx, testis, and thyroid. NHL was the only variant present in all the cases. Diffuse large B-cell lymphoma (DLBCL) was the most common variant present in 11 cases (37%). The DLBCL was found to be aggressive in most of the cases with most of them being activated B-cell type, ABC (70%) and rest being Germinal center B-cell type, GCB (30%). **Conclusion**: A broad spectrum of extranodal organs is involved in various subtype of lymphoma. This study concluded that ENLs can occur at any location. The fact that a lymphoma is a primary ENL may be a factor in the treatment plan and prognosis. The lymphoma subtype B cell or T cell type, and the primary organ or tissue of origin can all be important prognostic factors.

Key words: Lymphoma; Extra-nodal; Diffuse large B-cell lymphoma

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INTRODUCTION

Lymphomas are classified into two major categories, Hodgkin lymphoma (HL) and non-HL (NHL). HL has five subtypes: Nodular lymphocyte predominant, nodular sclerosis HL, mixed cellularity HL, lymphocyte rich HL, and lymphocyte depleted HL. NHLs are: B-cell and T-cell types, which are sub-classified into different subtypes using immunohistochemistry, according to the WHO classification.[1] At least one quarter of NHL arise from tissue other than lymph nodes and even from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas (ENL).[2,3] Since these tumors are numerous when considered together are widely distributed throughout the body, it is difficult to find adequate series of any given site. Moreover, many historical series were published before the recognition of mucosa-associated lymphoid tissue as the origin of many ENLs and in general, classification of primary ENLs was similar to that of nodal lymphomas,

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without consideration that their origin could be different. Hence, the literature lacks uniformity in histopathological classification. The first attempt to eliminate this problem was made only very recently with the proposal of the Revised European-American Lymphoid Neoplasms classification.[4] Primary ENLs, a heterogeneous group of diseases of diverse etiology, pathogenesis, pattern of presentation and outcome, account for up to 20% of all malignant lymphomas.[5] It refers to group of disorders arising from tissues other than lymph nodes. The incidence is increasing and is probably due to better diagnostic immunophenotyping and imaging modalities. The ENL shows distinctive clinical, radiological, and pathological features. Along with typical histomorphology, different subtypes of ENL show specific pattern of immunohistochemical markers to be of significant value in establishing a diagnosis of lymphoma and ascertaining the exact subtype.

The strictest definition states that to be considered for an extra-nodal, a lymphoma must be confined to a solitary extranodal site and its contiguous lymph node group at the time of diagnosis. However, this definition excludes cases that are clearly extranodal in origin from a pathological and radiological point of view, but that have undergone early dissemination to other lymph node groups or bone marrow.[6] In this article, we present 27 cases of primary ENL with reference to its clinical presentation, histomorphological picture, and immunohistochemistry, grouped in descending order of frequency.

Aims and objectives

The aim of the study was to study the prevalence of primary ENLs at unusual sites.

MATERIALS AND METHODS

A prospective study was conducted for a period of 3 years to study the prevalence of primary ENLs at rare sites.

Inclusion criteria

- In this study, all the biopsies with features suspicious of lymphoma clinically and cytologically were evaluated
- The H and E-stained slides of all the cases were reviewed by experienced pathologists with an aim to apply proper IHC panel to reach to a final diagnosis.

Exclusion criteria

- Paraffin embedded tissue blocks with sections from the non-representative areas and sections with quantitatively inadequate material for repeat H and E stain and immunohistochemistry were not included in the study
- Cases having infective and metastatic lesions were excluded from the study
- H and E-stained sections showing extensive histomorphological artifacts such as cautery/crush artifacts were also excluded from the study.

RESULTS

In our study, the participants were having a mean age of 50 years and showed a bimodal distribution. A total 16 cases were male (59%) and rest were female (11 cases, 41%). We found that B-symptoms were present in 19 cases (70%) and absent in the remaining. Most of the cases were of B- Cell type (20 cases, 74%) and rest were T-cell type (seven cases, 26%) (Chart 1).

The most common extranodal site being gastrointestinal tract (10 cases, 37%) followed by central nervous system (CNS) (four cases, 15%), spleen (two cases, 7%), tonsil (two cases, 7%), and cutaneous site (two cases, 7%). Other less common sites included breast, paranasal sinuses, mediastinum, floor of mouth, nasopharynx, testis, and thyroid (Table 1).

NHL was the only variant present in all the cases. Diffuse large B-cell lymphoma (DLBCL) was the most common variant present in 11 cases (37%). The DLBCL was found to be aggressive in most of the cases with most of them being activated B-cell like, ABC (70%) and rest being Germinal center B-cell like, GCB (30%). The ABC variant was found to be very aggressive with high proliferation index and positivity of MUM1.One such case of extranodal DLBCL and activated B-cell like was found in breast with MUM-1 positivity and high proliferation index (Figures 1-3). The GCB variant was somewhat less virulent as compared to the ABC variant and showed positivity for BCL6. We have described a case of a 71-year-old man with testicular DLBCL and activated B-cell like where the tumor cells

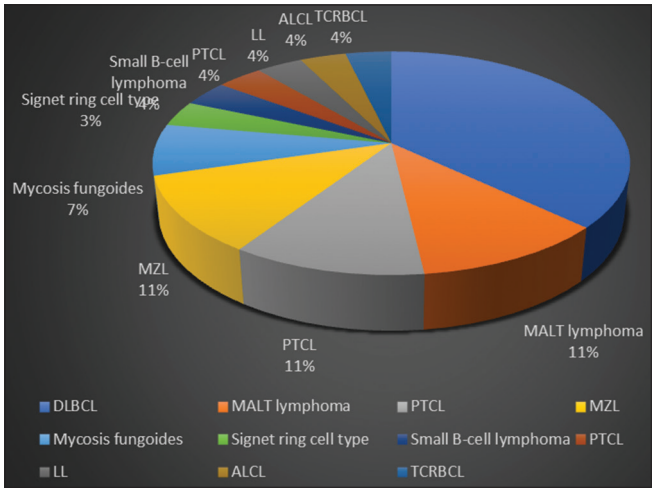

Chart 1: Distribution of different lymphoma variants

Table 1: Distribution of various subtypes of lymphomas

S. No.	Age	Sex	Site	Type	B- symptoms
1.	35	F	Nasopharynx	Extra-nodal marginal zone lymphoma	Absent
2.	42	F	Intestine	Diffuse large B-cell type, GCB	Present
3.	54	M	Stomach	Gastric lymphoma, B- cell Signet ring cell type	Present
4.	72	M	Spleen	Diffuse large B-cell lymphoma, ABC	Present
5.	71	M	Testis	Diffuse large B-cell lymphoma, GBC	Present
6.	70	M	Intestine	Peripheral T-cell lymphoma	Present
7.	20	M	SOL in frontal and parietal region	Diffuse large B-cell lymphoma, ABC	Present
8.	66	M	Tonsil	Extranodal marginal zone lymphoma	Absent
9.	65	M	Stomach	MALT lymphoma	Absent
10.	85	M	Spleen	Small B-cell lymphoma	Absent
11.	50	F	Floor of mouth	Peripheral T-cell lymphoma	Present
12.	74	F	Colorectal mass	MALT lymphoma	Present
13.	28	M	Ileocecal mass	Mantle cell lymphoma	Present
14.	59	F	Skin biopsy	Mycosis fungoides	Absent
15.	45	F	Thyroid lesion	MZL	Absent
16.	36	F	CNS	DLBCL, ABC	Present
17.	66	M	CNS	DLBCL, ABC	Present
18.	15	M	Mediastinal mass	PTCL	Present
19.	60	M	Cecal mass	DLBCL, ABC	Present
20.	60	F	Paranasal mass	TCRBCL	Absent
21.	45	F	Breast mass	Diffuse large B-cell lymphoma, ABC	Present
22.	30	F	Wrist swelling	Mycosis fungoides	Absent
23.	55	F	Antrum	DLBCL, ABC	Present
24.	5	M	Tonsil	Lymphoblastic lymphoma	Present
25.	54	M	Stomach	MALT lymphoma	Present
26.	40	M	Stomach	DLBCL, GCB	Present
27.	49	M	Frontal SOL	ALCL	Present

CNS: Central nervous system, MALT: Mucosa-associated lymphoid tissue, DLBCL: Diffuse large B-cell lymphoma, PTCL: Peripheral T-cell lymphoma

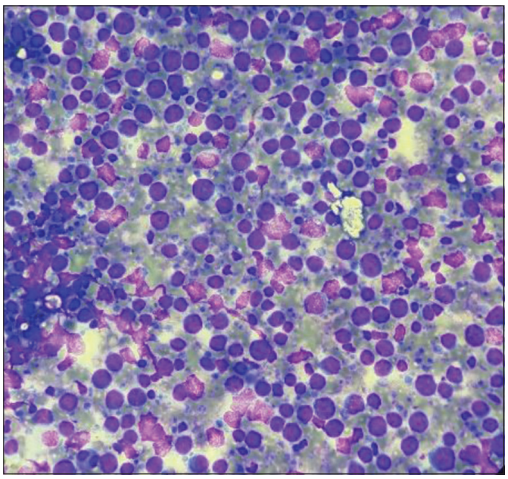

Figure 1: Diff-quik stain-Large atypical cells on cytology smears

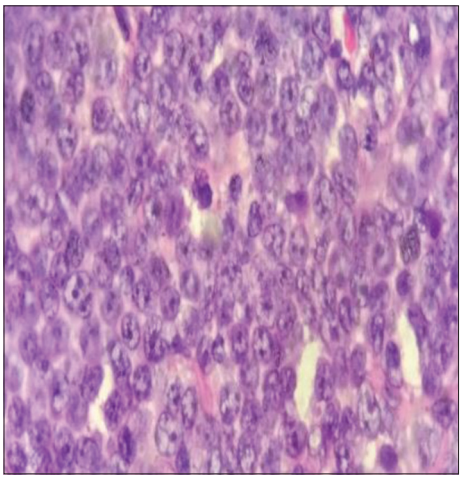

Figure 2: H and E (×40) large cells with high mitotic count

showed positivity for CD45, CD20, and were negative for MUM1 (Figures 4-7).

After DLBCL, the second most common variant was mucosa-associated lymphoid tissue (MALT) lymphoma (11%) which was associated with gastritis caused by *Helicobacter pylori*. The presence of *H. Pylori* was confirmed by serological tests which show 97.6% sensitivity and 96.2% specificity. Similar incidence was reported in peripheral T-cell lymphoma which showed poor response to treatment (Figures 8-12).

One less common variant which we encountered in our study was primary gastric lymphoma and signet ring cell type (3%). It is an unusual variant of NHL (Figures 13-17). Three of the cases were diagnosed as marginal zone lymphoma (11%), sites being nasopharynx, thyroid, and tonsil. Usually, extranodal marginal zone lymphoma is a diagnosis by exclusion. Other variants included small B-cell lymphoma (4%) with a circulating component CLL/SLL. It was somewhat less aggressive and showed better response to treatment. Mantle cell lymphoma occurred at uncommon location, site being ileocecal region, and showed positivity

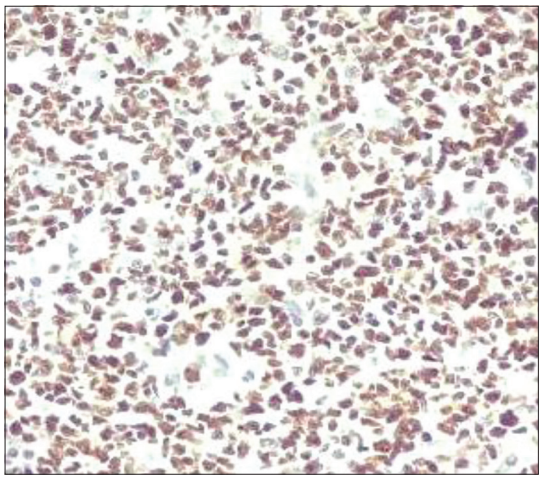

Figure 3: MUM1 positivity

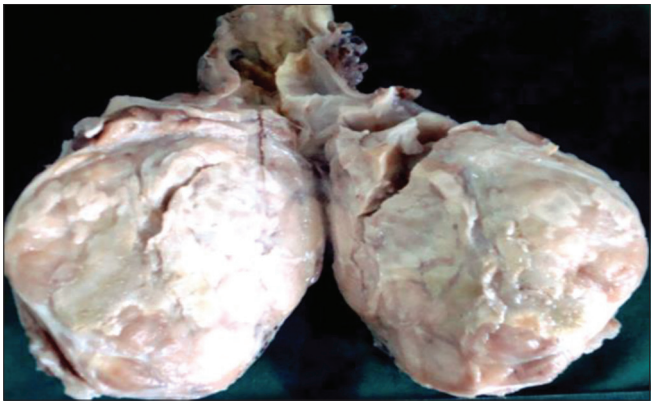

Figure 4: Bilateral orchidectomy specimen

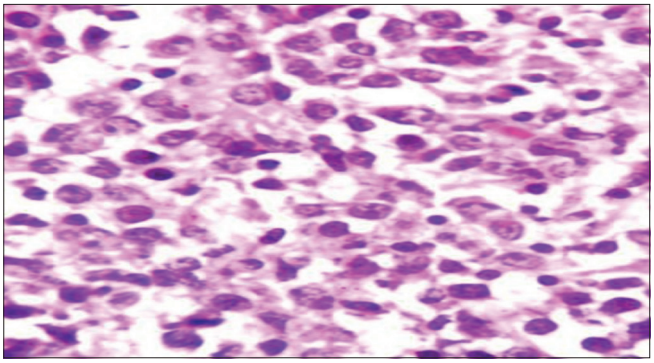

Figure 5: Large pleomorphic tumor cells

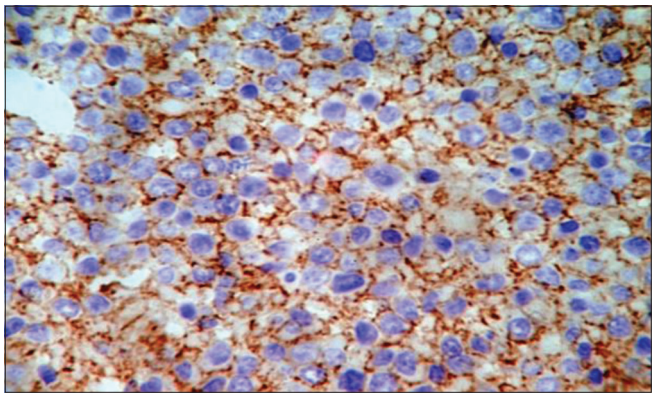

Figure 6: Tumor cells showing positivity for LCA

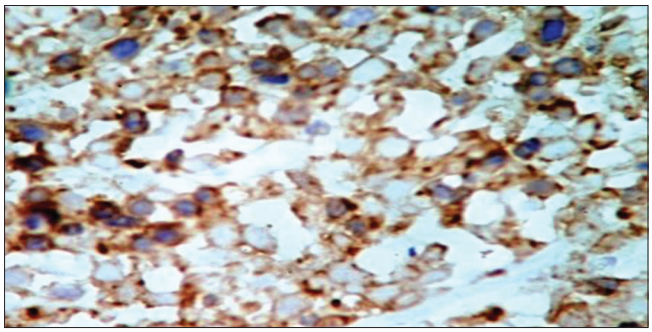

Figure 7: Membranous staining for CD20

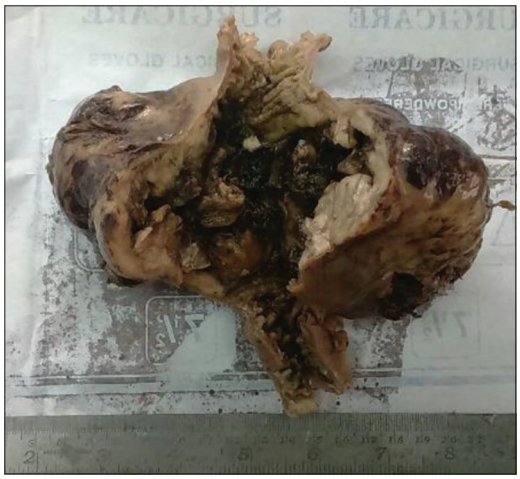

Figure 8: Grey white tumor in gross specimen

for CD20, CD5, and CyclinD1. We got a single case of T- cell lymphoblastic lymphoma in a 5-year-old male child and it was very aggressive with very high proliferation rate (Ki67 >90%). Other variants included T-cell rich B-cell lymphoma and ALCL in CNS (Figures 18-21).

DISCUSSION

In our study, the most common primary ENL encountered was DLBCL (37%) and the most common site involved was gastrointestinal tract (40%). A study by AlShemmari et al.,[7] also showed the most common histologic subtype among extranodal cases was DLBCL, which accounted for 71% (69) of cases. The most common anatomic site involved was the gastrointestinal tract, which accounted for 45% of all cases. After gastrointestinal tract CNS was most commonly involved by DLBCL. The incidence of DLBCL as primary CNS lymphoma (PCNSL) has increased sharply in the past three decades. In a study by Raoux et al.,[8] it was reported that most PCNSL cases are DLBCLs. We present a single case of PCNSL where a 49 male presented with

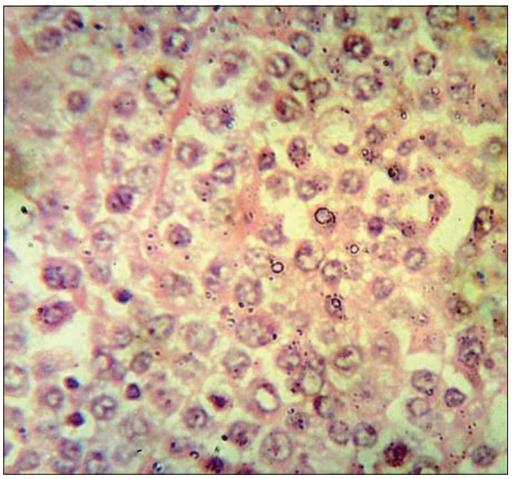

Figure 9: H and E (×40) Large pleomorphic tumor cells

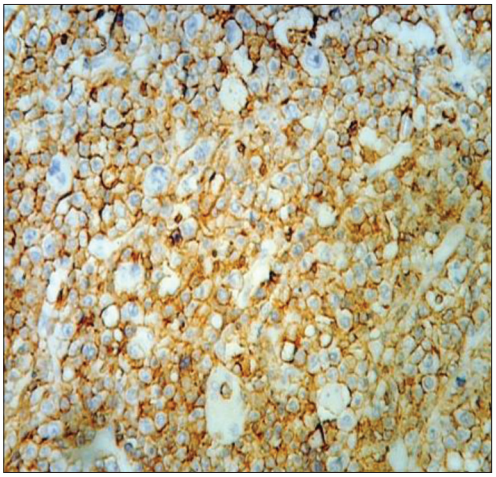

Figure 10: Membranous staining for CD45

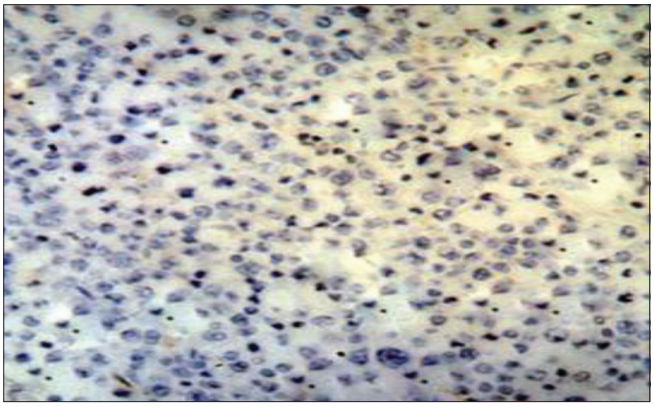

Figure 11: Tumor cells negative for CD20

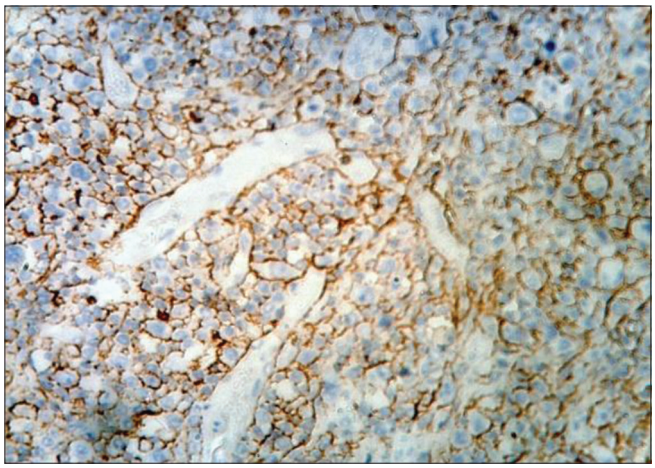

Figure 12: Membranous staining for CD3

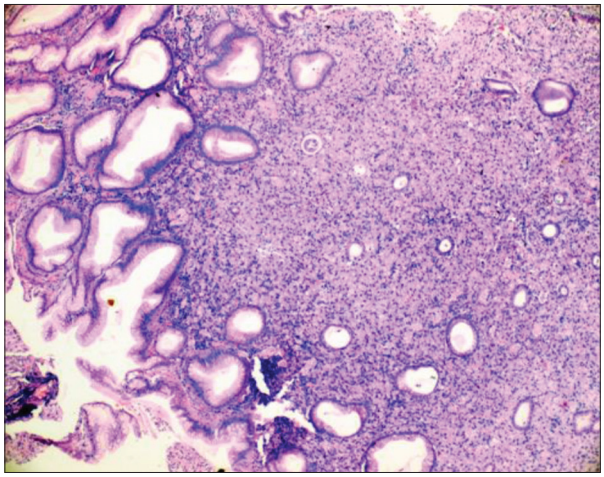

Figure 13: Lamina propria shows large tumor cells

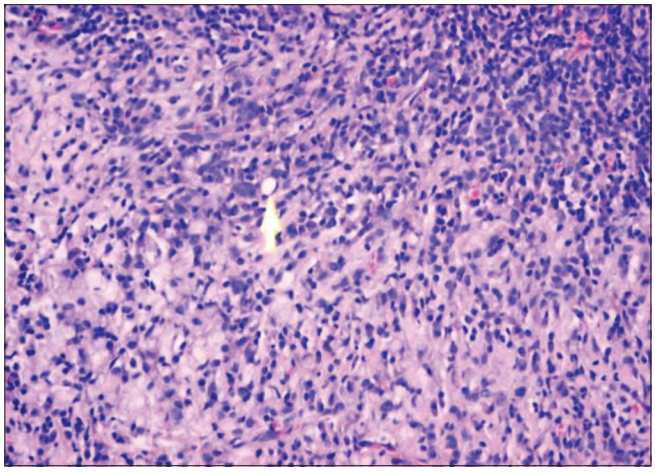

Figure 14: Signet ring (large cytoplasmic mucin droplet pushing the nucleus to periphery

frontal and parietal space occupying lesion on MRI and rapidly deteriorating condition. On histopathology, it was a large cell lymphoma which was thought to be of DLBCL type. It turned out to be anaplastic large cell lymphoma after the application of panel of immunohistochemical markers. The tumor cells showed positivity for CD5 and ALK.

Although rare but ALCL can present as primary ENL in CNS. Similar findings have been reported by George et al.[9] In another instance, a middle-aged lady came for FNAC with complaint of lump in the upper inner quadrant of

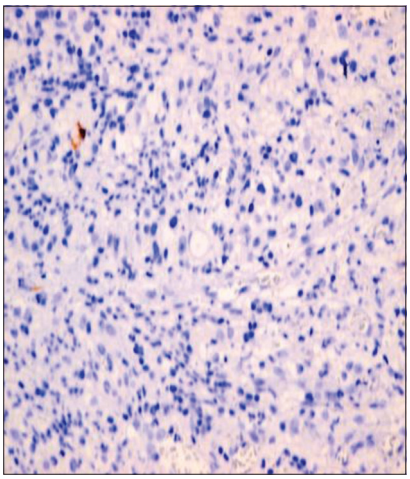

Figure 15: Tumor cells negative for CK20

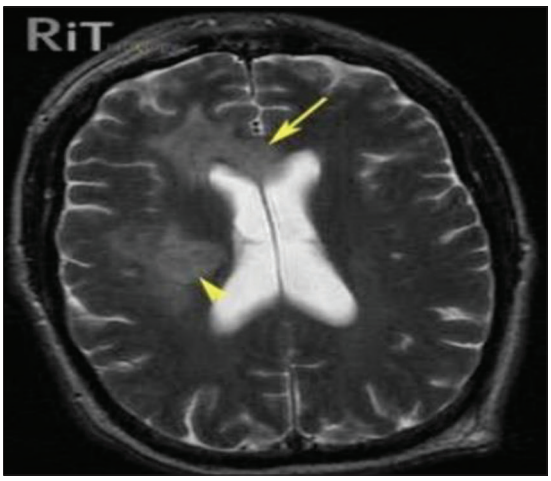

Figure 18: Frontal and parietal space occupying lesion

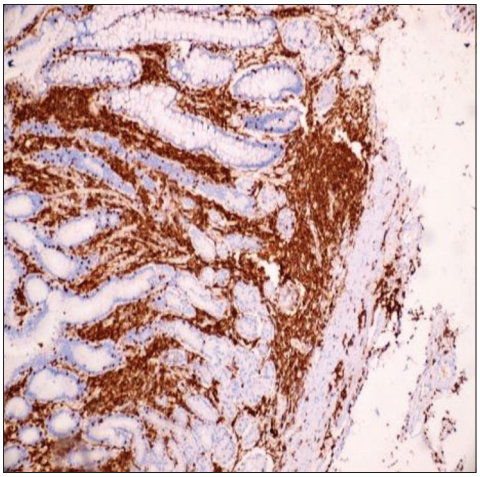

Figure 16: CD45-Strong and diffuse positivity

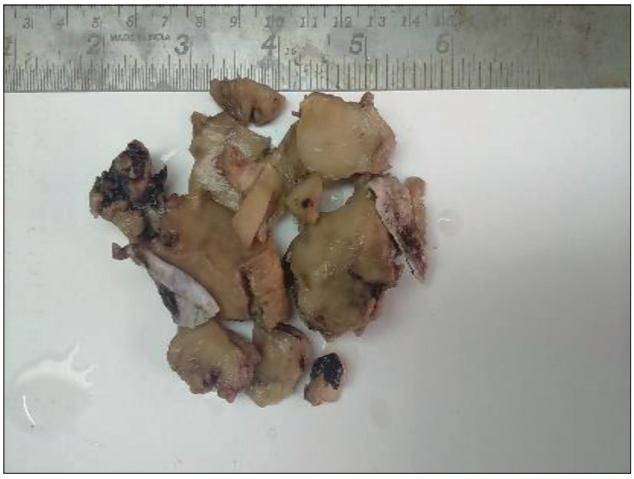

Figure 19: Gross received as multiple grey white tissue bits

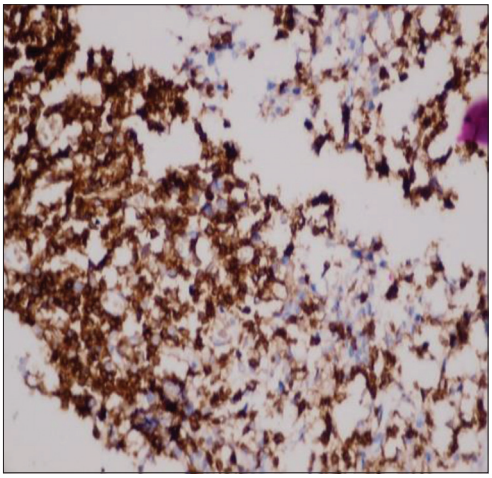

Figure 17: Tumor cells positive for CD20

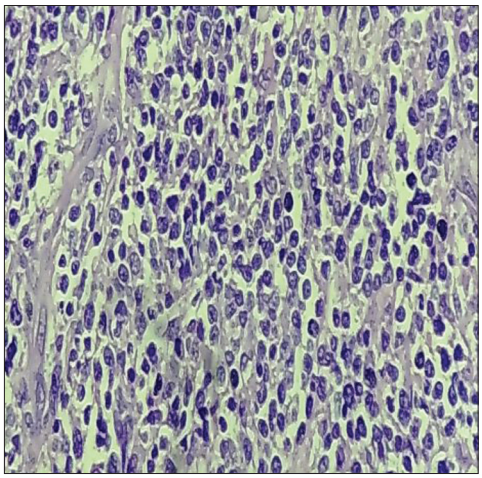

Figure 20: H and E (10×) Large pleomorphic tumor cells

left breast in the past 3 months. She also complained of drenching night sweats, unintentional weight loss, and fever on and off. She had undergone FNAC previously in some other hospital and was given a diagnosis of Intramammary reactive lymph node. As her symptoms did not subside, she decided to undergo a repeat FNAC in a different setup. The prepared cytology slides were stained by Diff-Quik stain and examined under microscope. It showed hypercellular

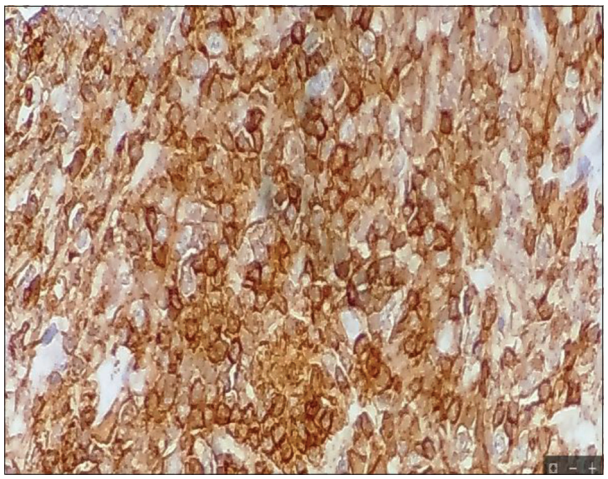

Figure 21: ALK positivity in tumor cells

smears with presence of dissociated monomorphic large atypical lymphoid cells with high nuclear cytoplasmic ratio, vesicular chromatin, and prominent nucleoli. There was presence of lymphoglandular bodies in the background (Figure 5). We gave a diagnosis suggestive of large cell lymphoma. Later, on in biopsy, there was diffuse effacement of normal tissue architecture by large atypical cells with vesicular chromatin and prominent nucleoli. The tumor cells showed positivity for CD20 and MUM1. The case was reported as DLBCL, ABC type. Prognosis could not be ascertained due to loss of follow-up. Other extranodal site included splenic small B-cell lymphoma with predominant red pulp involvement. Similar findings were reported by Mollejo et al.[10]

Ahmad et al.,[11] have documented that primary testicular NHL comprises around 9% of testicular cancers and 1–2% of all NHL. It primarily affects older men, with a median age at presentation of around 67 years. Our case series have a reported case of testicular DLBCL, GCB type in a 71-year-old male who presented to the surgery OPD with scrotal swelling for the past 3 months, which was rapidly increasing in size. There was associated history of weight loss and anorexia. Ultrasound showed enlargement of testis with diffusely heterogeneous hypoechoic parenchymal echotexture. Bilateral orchidectomy was done. On histopathology, there was presence of large tumor cells which showed positivity for CD45, CD20, and were negative for MUM1.

We found three cases of mucosa associated lymphoid tissue two being present in stomach and one presented as colorectal mass. There was presence of *H. pylori* in the participants which was confirmed by serological tests. Farinha and Gascoyne[12] have also documented strong association between MALT lymphoma and *H. Pylori*. Rarely MALT lymphoma can affect colon. Abbas et al.,[13] have reported a single case report of MALT lymphoma in colon.

Signet-ring cell lymphomas are rare especially as primary gastric tumors. We have included a single case of Gastric B- cell signet ring cell lymphoma. A 54-year-old male presented with pain in abdomen and anemia. On examination, no hepatomegaly or lymphadenopathy was present. Upper GI endoscopy showed large nodular ulceroproliferative neoplasm seen just below Gastroesophageal junction over lesser curvature involving cardia and proximal body, suggestive of carcinoma stomach. Computerized tomography scan showed a mildly enhancing mucosal growth over body of stomach toward lesser curvature along with gastric lymphadenopathy and findings suggestive of carcinoma stomach with perigastric lymphadenopathy. The biopsy showed neoplastic cells distributed uniformly with clear cytoplasm and the nucleus squeezed to the side mimicking the appearance of signet ring in morphology. In immunohistochemistry, the tumor cells were negative for Ck20, CD3 and showed strong and diffuse positivity for CD45, CD20. Tungekar[14] have documented a case of primary gastric B-cell lymphoma. Very often artifactual signet ring like cells in endoscopic biopsies can be confused by signet ring cell lymphomas. Hence, it is very important to use histomorphology and immunohistochemistry concurrently to reach to a valid and conclusive diagnosis.

A 5-year-male child presented with difficulty in swallowing and breathing 5 months back with a tonsillar enlargement. On examination, Grade 4 tonsillar hypertrophy was present. Clinically, it was suspected to be Burkitt's lymphoma. The previous biopsy was suggestive of B-cell NHL. However, the tumor cells showed Indian file arrangement on histopathology along with positivity for CD3, Tdt with very high proliferation rate Ki67 >95%. It was reported as T-cell lymphoblastic lymphoma. One case was of mantle cell lymphoma present in ileocecal region. Tumor cells showed positivity for cyclinD1. Two cases were reported to be of Mycosis fungoides. Immunohistochemistry was more helpful to exclude other lymphomas than to confirm a diagnosis of mycosis fungoides. Three cases were of peripheral T-cell lymphoma sites being gastrointestinal tract, floor of mouth, and mediastinum. We had received segment of intestine with the presence of a firm and grey-white tumor. On histopathology, there was presence of large atypical cells having high nuclear cytoplasmic ratio, vesicular chromatin, and prominent nucleoli. The tumor cells showed positivity for CD45, were negative for CD20, and strongly and diffusely positive for CD3. The case was reported as peripheral T-cell lymphoma (PTCL). PTCL although have been reported in gastrointestinal tract but mediastinal location is somewhat rare. In our case, the

tumor cells showed positivity for CD5, CD15 and CD30. Kakuta et al.,[15] have reported case of mediastinal peripheral T-cell lymphoma. Similarly, PTCL in oral cavity is a rare finding. Sirsath et al.,[16] have reported occurrence of PTCL in oral cavity.

Limitations of the study

Immunophenotyping, although indispensable in the diagnosis and classification of hematopoietic and lymphoid neoplasms, has to be used cautiously with knowledge of the antibodies used. No antigen is totally lineage or lymphoma specific, and for this reason, immunostaining must be performed in the context of a panel.

CONCLUSION

This study concluded that ENLs can occur at any location. In our study, the most common site was gastrointestinal tract, followed by CNS and spleen. Other less common sites included breast, testis thyroid, paranasal sinuses, mediastinum, floor of mouth, cutaneous location, and nasopharynx. All the cases were exclusively of non-Hodgkin's type. Primary B-cell ENLs are more common than T-cell lymphoma. DLBCL was the most common NHL encountered. Incidence of extranodal disease is rising.[17,18] Various factors have been attributed to this changing trend of lymphoma, namely, HIV, increasing use of immunosuppressive therapy and indolent viral infection.

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