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CASE SERIES

A Case Series on Extranodal Non-Hodgkin's Lymphoma

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Abstract

Introduction: Non-Hodgkin's lymphoma is broadly classified into B- and T-cell lymphomas. Accurate diagnosis and classification are essential for the appropriate management and prognostication of lymphomas. **Aim and Objectives:** To analyse the histopathological spectrum of extra nodal Non-Hodgkin's lymphomas encountered in the series and to evaluate the utility of immunohistochemistry in the classification of extra nodal Non-Hodgkin's lymphomas. **Methodology:** This is a descriptive study which includes seven cases of extranodal lymphomas that were reported in the Department of Pathology, Coimbatore Medical College, Coimbatore, over a period of one year, from March 2024 to March 2025. **Results and Discussion:** Seven cases included in this study were from seven different sites, like Eyelid, Central Nervous System, Scalp, Spleen, Thyroid, Anal canal and Parapharyngeal wall. The most common type of extra nodal non–Hodgkin's lymphoma in this study was Diffuse Large B-Cell Lymphoma (3 cases), constituting 43%, followed by Plasmablastic Lymphoma (2 cases), constituting 29% and Anaplastic large cell lymphoma (1 case) and Marginal Zone Lymphoma (1 case), each constituting 14%. **Conclusion:** Most of the extra nodal Non-Hodgkin lymphomas confer a worse prognosis than their nodal counterpart. So early diagnosis and treatment are essential. Histopathological diagnosis plays a vital role in identifying these tumours in rare sites.

Keywords: Anaplastic Large Cell Lymphoma, Diffuse Large B-Cell Lymphoma, Extra Nodal Non-Hodgkin Lymphoma, Marginal Zone Lymphoma, Plasmablastic Lymphoma

1. Introduction

Non-Hodgkin's lymphoma is the tenth most common cancer affecting the population worldwide. The incidence of Non-Hodgkin's lymphoma is 553,389 cases per year worldwide and 39,736 cases per year in India[1]. Non-Hodgkin's lymphoma is broadly classified into B- and T-cell lymphomas. Accurate diagnosis and classification are essential for the appropriate management and prognostication of lymphomas. This can be achieved by the integration of histopathology, immunohistochemistry, flow cytometry and molecular tools like fluorescent *in situ* hybridisation and next-generation sequencing.

2. Aim and Objectives

- To analyse the histopathological spectrum of extra nodal Non-Hodgkin's lymphomas encountered in the series.
- To evaluate the utility of immunohistochemistry in the classification of extranodal Non-Hodgkin's lymphomas.

3. Review of Literature

According to Swami R, *et al*, a total number of seventeen cases of primary extra nodal non-Hodgkin's lymphoma were included in the case series and

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discussed the anatomic distribution, clinical features, Immunohistochemical typing and the outcome of these cases. The majority of these patients were in the sixth decade of life, and the age range was wide, between 5-92 years. Male: female ratio of the cases included in this study was 2.4:1. In this study, Nasopharynx (4/17) was the most common site of extra nodal non-Hodgkin's lymphoma, constituting about 25.3% followed by retroperitoneal masses (3/17), constituting 17.6%. Diffuse large B-cell lymphoma (8/17) was the most common histological subtype found in this case series[2].

According to Gurwale S, *et al*, a total of thirteen cases were included in the study, and the diagnosis was made based on the histopathology and immunohistochemical staining. In this study, the head and neck were the predominant region of involvement, which included five cases, followed by genital organs (three cases), the central Nervous System (CNS) and thyroid (two cases each). This case series also includes extra nodal non-Hodgkin's lymphoma of the adrenal gland, nasal cavity, and skin. This study also included very rare cases of lymphomas at unusual sites, such as plasmablastic lymphoma in the anorectal region and Burkitt's lymphoma primarily involving the ovary. Most of the cases included in this study were Diffuse Large B-Cell Lymphoma[3].

4. Materials and Methods

Study Design: Descriptive study
Study Period: A period of 1 year from March 2024 to March 2025.
Study Place: Department of Pathology, Coimbatore Medical College, Coimbatore.
Sample Size: Seven cases. (Table 1)

4.1 Methodology

Seven cases of extranodal lymphomas that were reported in the Department of Pathology, Coimbatore Medical College, Coimbatore, over a period of one year from March 2024 to March 2025 were included and reviewed in this study.

5. Results (Including Observations)

Three out of seven cases (43%) included in this study were males, and four (57%) were females (Chart 1). The majority of cases (four) included in this study were between 40–50 years of age, constituting about 57%. Seven cases included in this study were from seven different sites, like Eyelid, Central Nervous System, Scalp, Spleen, Thyroid, Anal canal and Parapharyngeal wall (Chart 2). The most common type of extra nodal non–Hodgkin's lymphoma in this study was Diffuse Large B-Cell Lymphoma (3 cases), constituting 43%, followed by Plasmablastic lymphoma (2 cases), constituting 29% and anaplastic large cell lymphoma (1 case) and marginal zone lymphoma (1 case), each constituting 14% (Chart 3).

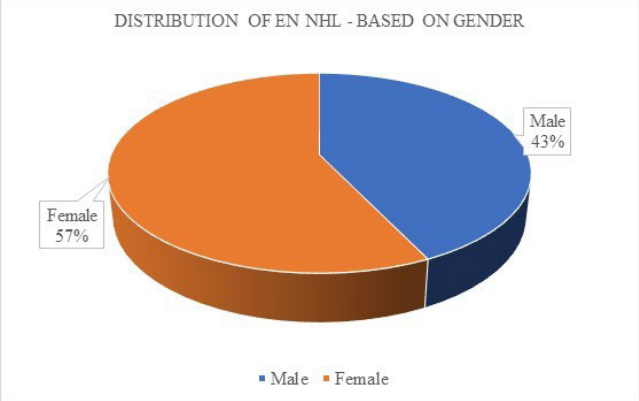

Chart 1. Distribution of EN NHL - Based on gender.

Table 1. Details of the 7 cases included in the study

Case No.	AGE	GENDER	SITE	DIAGNOSIS	HPE No.
1	44	Male	Eyelid	Plasmablastic Lymphoma	925/24
2	44	Male	Anal Canal	Plasmablastic Lymphoma	2240/24
3	64	Male	CNS	DLBCL	2678/24
4	40	Female	Parapharyngeal Space	DLBCL	2469/24
5	82	Female	Thyroid	DLBCL	3722/24
6	11	Female	Scalp	ALCL	2576/24
7	42	Female	Spleen	Marginal Zone Lymphoma	827/25

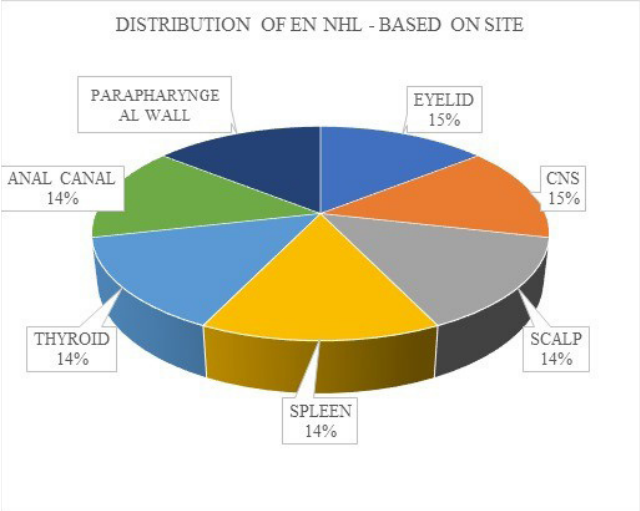

Chart 2. Distribution of EN NHL - Based on site.

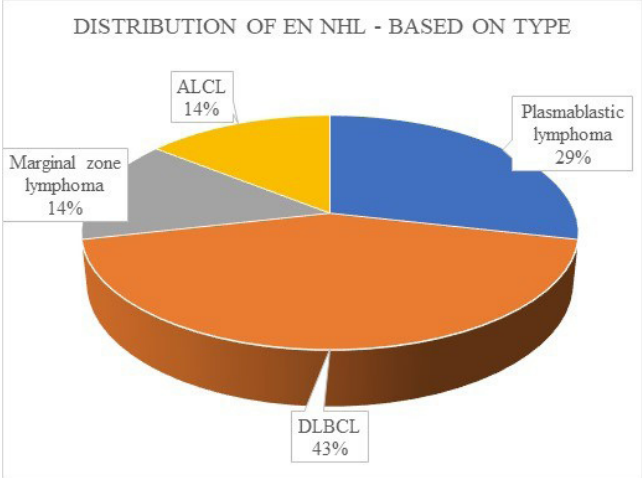

Chart 3. Distribution of EN NHL - Based on the type of EN NHL.

6. Discussion

Extra Nodal Lymphomas (ENL) are a heterogeneous group of lymphomas that arise from tissues other than the lymph node or the sites devoid of lymphoid tissue. Extra nodal lymphomas are of two types: primary and secondary. They are a diagnostic challenge to clinicians and pathologists due to varied epidemiology, morphology, clinical presentations, and aetiology. The most common histological type of ENL noted is Diffuse Large B-Cell Lymphoma type (DLBCL), followed by peripheral T-cell lymphoma and Mucosa-Associated Lymphoid Tissue Lymphoma (MALToma)[4].

Extra nodal lymphoma is said to be primary if it meets the following criteria laid by Dawson *et al.* It includes

- Absence of palpable lymphadenopathy
- Absence of mediastinal lymphadenopathy on X-ray of the chest
- Presence of lesion at extranodal site
- Involvement of lymph nodes in the areas adjacent to the primary lesion
- Normal white blood cell count[5].

The secondary ENL is the presentation of lymphoma first in lymph nodes and involving the extra nodal sites subsequently[6].

Case no. 1

A 44-year-old male, who is a known HIV patient on anti-retroviral therapy, presented to the Ophthalmology (OPD) with a growth in the upper eyelid of size 2*1.7cm for 1 1-month. Another growth was also found in the anterior hard palate measuring 3*2.2cm. (Figure 1) An incisional biopsy was taken from the growth in the eyelid.

Grossly, received multiple grey white to grey brown soft tissue bits measuring in toto 0.7*0.5cm. Microscopy revealed diffuse infiltration of large plasmacytoid cells with vesicular nuclei and prominent nucleoli, admixed with a few mononucleate and binucleate plasma cells. There was brisk mitotic activity. (Figure 2)

Figure 1. Case no. 1 with growth in the eyelid and hard palate.

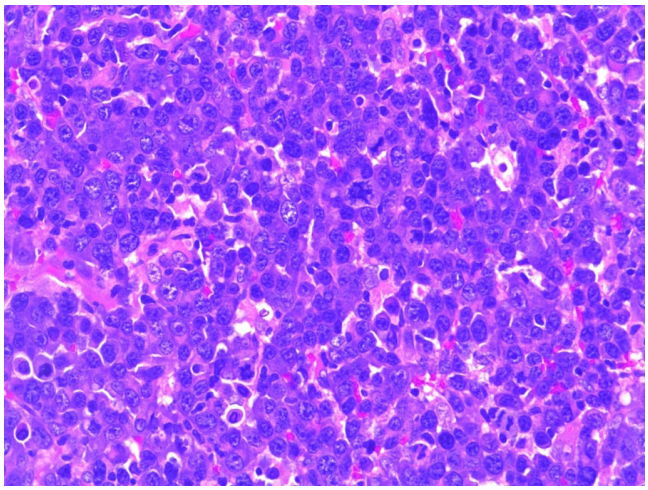

Figure 2. Case no.1(925/24)- Cells with eccentric nuclei and prominent nucleoli in a few cells, admixed with plasma cells. Plasmablastic lymphoma(Hand E) (40X).

Immunohistochemistry showed membranous positivity for CD138, diffuse, strong nuclear positivity for MUM1. PAX 5 was negative. (Figures 3 and 4)

Based on the morphology and immunohistochemistry, a diagnosis of Plasmablastic Lymphoma was made.

Case no. 2

A 44-year-old male presented with swelling in the anal region for the past month. There was no history of pain or bleeding in the rectum. He was a known person living with HIV/AIDS (PLHA) and a Hepatitis C virus-positive case on treatment. Magnetic Resonance Imaging (MRI) pelvis impression was given as Anal canal growth with extension into bilateral ischioanal fossa, perineal skin up to the gluteal cleft, with regional lymph node metastasis.

An edge wedge biopsy was taken. Multiple grey white to grey brown soft tissues measuring 2*0.5cm were received.

Microscopy revealed dyscohesive sheets of round to oval cells with a moderate amount of cytoplasm, eccentrically placed nuclei with vesicular nuclei and prominent nucleoli. Tumour cells extended up to the anal mucosa. A few mature plasma cells were also seen.

Immunohistochemistry revealed diffuse positivity for CD138 and MUM1.

Based on the morphology and immunohistochemistry, a diagnosis of Plasmablastic Lymphoma was made.

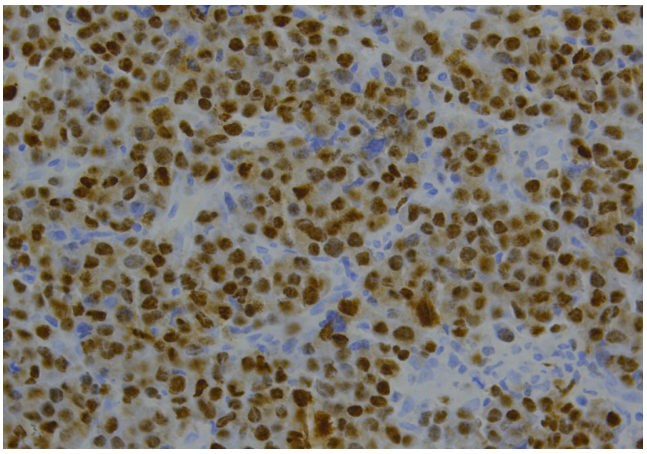

Figure 3. Case no.1(925/24) – Immunohistochemical staining for MUM1(positive)

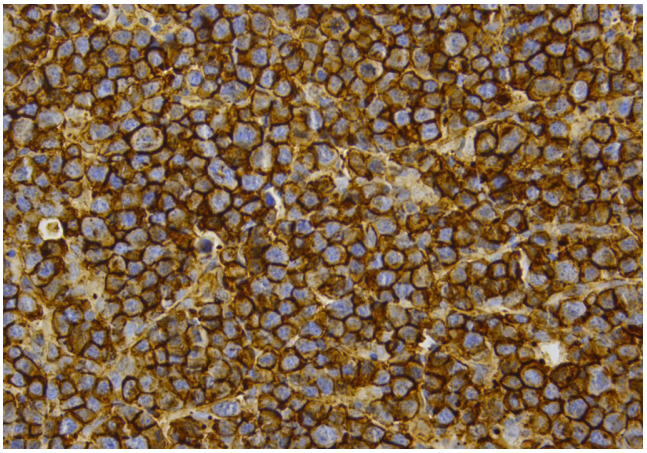

Figure 4. Case no.1(925/24) – Immunohistochemical staining for CD138 (positive).

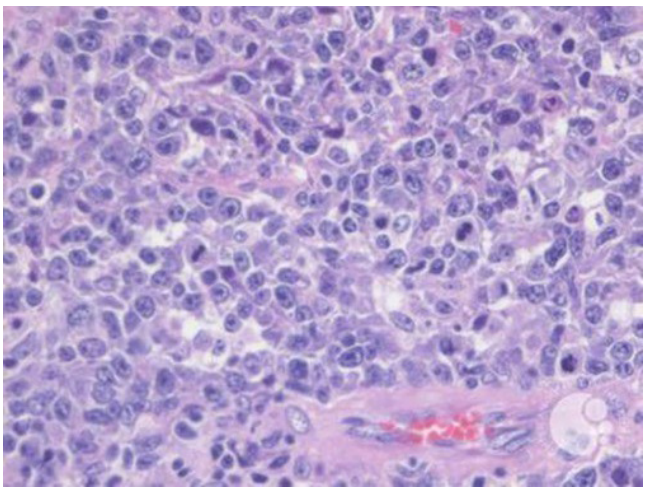

Figure 5. Case no. 3 (2678/24)- Sheets of atypical lymphoid cells with angiocentric pattern – Primary CNS DLBCL (H and E) (40X).

Plasmablastic lymphoma is commonly seen in HIV patients and immunodeficiency states. It occurs in nodal and extranodal sites, predominantly the oral cavity and other rare sites like the gastrointestinal, skin, bone, nasal and paranasal sinus, and orbit. Tumour cells are Epstein-Barr Virus (EBV)-positive in most cases. Frequent c- Myelocytomatosis (MYC) translocations are seen. The morphological spectrum varies from cells with diffuse and cohesive proliferation to cells with plasmacytic differentiation. The differential diagnosis includes plasmablastic plasma cell myeloma and Large B-cell lymphoma. The prognosis is generally poor. Anti-retroviral treatment plays a key role in deciding the chemotherapy[7].

Case no. 3

A 64-year-old male presented with complaints of seizures on and off for the past month. MRI brain showed a lesion of size 4.4*3.3*3.6cm in the left capsuloganglionic region with extension along the left midbrain, with diffuse surrounding oedema with mass effect over the left lateral ventricle. A similar lesion of size 2.4*2.6*2.3 cm was noted in the left frontal region with T2 heterointense and T1 hypointense. In contrast, the lesion shows peripheral homogenous enhancement with a central non-enhancing area. Impression was given as intraxial lesion in the left capsuloganglionic region with significant restriction, with differential diagnosis of Primary CNS Lymphoma / Metastasis – Suggested primary evaluation.

Squash cytology was done, which showed highly cellular smears composed of medium to large-sized dispersed malignant lymphoid cells having scant cytoplasm with granular chromatin and irregular nuclear membrane. Brisk mitotic activity and necrosis were seen. Impression was given as features suggestive of high-grade lymphoma.

Tissue was also given for histopathological examination. Grossly, received multiple grey white to grey brown soft tissue bits measuring 2.5*1.8 cm. Microscopic examination revealed a dispersed population of large, round to oval cells having scant to moderate cytoplasm with round to lobulated vesicular nuclei and inconspicuous to small nucleoli. They are admixed with small lymphocytes and histiocytes. Perivascular cuffing of the tumour cells was seen. Vascular invasion was not seen. (Figure 5)

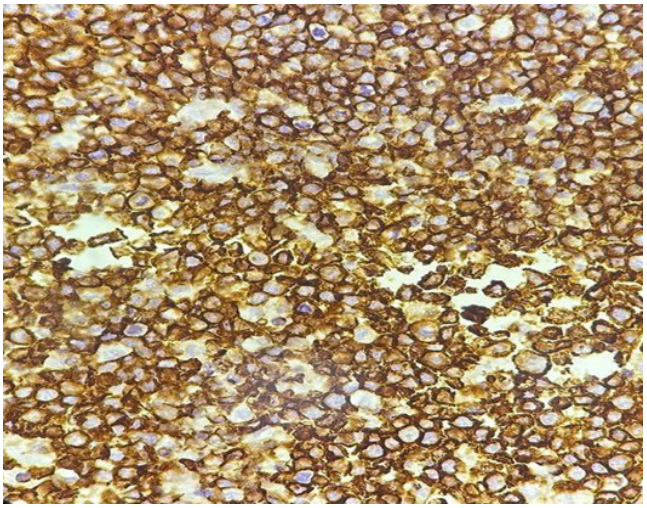

Figure 6. Caseno.3(2678/24) –Immunohistochemical staining for LCA (positive).

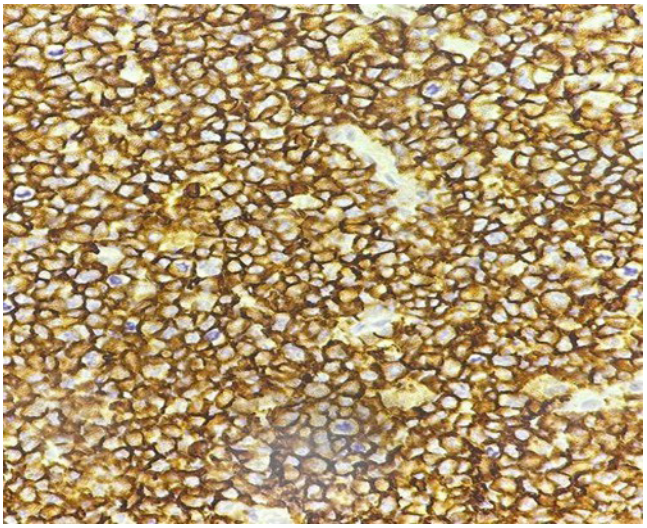

Figure 7. Caseno.3(2678/24) –Immunohistochemical staining for CD20 (positive).

Immunohistochemistry revealed diffuse and strong membranous positivity for LCA and CD 20. Ki67 index was 70%. (Figures 6 and 7)

Based on the morphology and immunohistochemistry and correlating with the imaging details, a diagnosis of Primary CNS Diffuse Large B-cell lymphoma was made.

Primary CNS Lymphoma can arise in the brain, spinal cord, leptomeninges, or eyes, without evidence of disease elsewhere in the body. Most common sites are the cerebral hemispheres, thalamus and basal ganglia, corpus callosum and periventricular region. 65% occur as solitary lesions, and the rest occur as

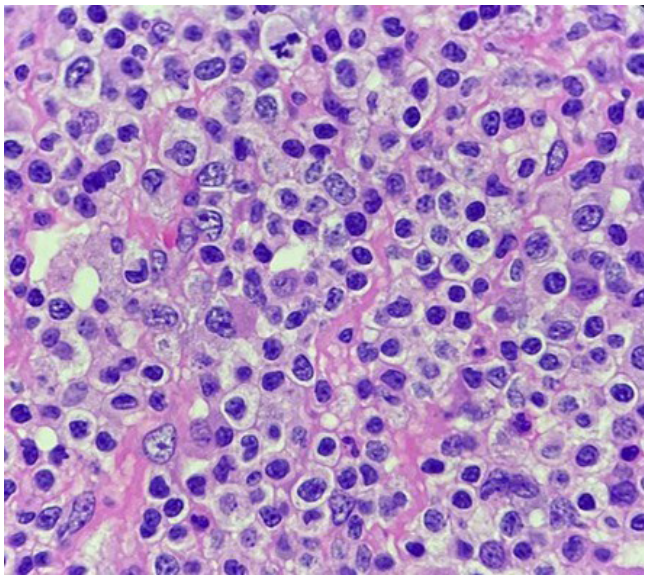

Figure 8. Case no. 6 (2576/24)- Large cells with horseshoe-shaped nuclei seen. ALCL (H and E) (40X).

multifocal lesions. They are aggressive and confer a worse prognosis than systemic DLBCL[8].

Case no. 4

A 40-year-old female presented with a swelling in the left parotid region and difficulty in swallowing for the past 1 month.

MRI reveals a fairly well-defined lesion in the left prestyloid parapharyngeal space extending posteriorly to the carotid space. The lesion causes medial displacement of the carotid artery. The lesion measures 7.3*5.1*7cm, extending from C2 to C5 levels. Impression was given as suggestive of neoplastic aetiology. Differentials – pleomorphic adenoma and neurogenic tumour (less likely).

Fine needle aspiration cytology was done from the lesion, and the features were suggestive of the following possibilities: i) Lymphoproliferative disorder, ii) Poorly differentiated carcinoma.

Trucut biopsy was done from the lesion. Grossly received multiple grey white soft tissues measuring 1.5*0.3cm.

Microscopy revealed sheets of round to oval cells having moderate eosinophilic cytoplasm with pleomorphic vesicular nuclei and prominent nucleoli. A few hyalinised blood vessels are seen. The cells are seen infiltrating the adipose tissue and muscle bundles.

Immunohistochemical examination revealed diffuse and strong positivity for CD45 and CD20 in the atypical lymphoid cells, Ki67 60-70% among atypical lymphoid cells, c-MYC 40 -50% positive among atypical lymphoid cells, Bcl 6 – 60-70% among atypical lymphoid cells, CD10–positive among atypical lymphoid cells, MUM1 – MUM1-positive among atypical lymphoid cells. Bcl2 – negative and CD3 – positive in background reactive T lymphocytes.

With this morphology and immunohistochemical findings, a diagnosis of Diffuse large B cell lymphoma, Germinal centre B cell type was made.

Para-Pharyngeal Space (PPS) tumours include a heterogeneous group of neoplasms, accounting for approximately 0.5–1.5% of all head and neck tumours. Salivary gland tumours comprise the majority of parapharyngeal space tumours, followed by neurogenic tumours and paragangliomas. Pleomorphic adenoma is the most common neoplasm. Primary malignant lymphoma of the parapharyngeal space is extremely rare. They are described as either isolated cases or small series of tumours in that space. Surgical approach is the preferred treatment modality for parapharyngeal space tumours. In contrast, radiotherapy for low-grade lymphoma and chemotherapy with or without radiotherapy are the preferred treatment modalities. Thus, it is very crucial in differentiating other tumours from lymphomas for appropriate treatment strategies[9].

Case no. 5

An 82-year-old female presented with pain and swelling in the anterior aspect of the neck for the past 2 months. Patient is known to be hypothyroid on regular treatment. Examination revealed a 5*4cm firm to hard swelling in the anterior aspect of the neck. With a clinical suspicion of thyroid carcinoma/lymphoma, a Tru-Cut biopsy was done.

Grossly, received seven linear cores of soft tissue measuring 1*0.5cm.

Microscopic examination revealed cords of small to medium-sized, round to elongated cells with indistinct cytoplasmic borders, vesicular nuclei and prominent nucleoli. Some cells show an irregular nuclear membrane.

Immunohistochemistry revealed diffuse and strong positivity of CD45 and CD20, Ki67 index 70%. Cytokeratin and TTF 1 – Negative.

Based on this morphology and immunohistochemistry, a diagnosis of high-grade B-cell Non-Hodgkin lymphoma – possibly Diffuse large B-cell lymphoma was made.

Diffuse large B-cell lymphoma of the thyroid constitutes 2.5% of extranodal lymphoma and 4 - 5% of thyroid malignancies. It is the most common type of lymphoma in the thyroid region. Usually arises on a background of Hashimoto thyroiditis or lymphocytic thyroiditis. It should be suspected in a rapidly enlarging thyroid nodule. Treatment of thyroid lymphoma depends on the histological subtype and the stage of the disease. It confers a worse prognosis than MALT lymphoma, which is the 2nd common type of thyroid lymphoma[10].

Case no. 6

A 11-year-old female child presented with a scalp swelling of size 4*4 cm for the past 6 months. CT imaging impression was given as Dermoid cyst of scalp with bony indentation involving erosion of the outer table of skull.

Excision biopsy of the swelling was done. Grossly, received two globular soft tissue masses, one measuring 2.5*2*1cm and the other measuring 2*1.5*1 cm and a single cystic structure measuring 2*1.5*0.1cm. Cut surface of the globular mass – grey white to grey tan with a solid, firm surface. No pultaceous material was made out grossly.

Microscopic examination revealed fragments of a lymphoid neoplasm with sheets and cords of medium to large lymphoid cells with irregular to folded and reniform, vesicular nuclei, moderate pale amphophilic cytoplasm and prominent nucleoli. They are admixed with histiocytes, small lymphocytes and a few plasma cells. No necrosis / normal nodal tissue seen. (Figure 8)

Immunohistochemistry was done. CD3 – negative, CD20 – negative, CD4 – positive,

CD8 - negative, ALK – positive, CD30 – positive, CD1a and S100 – negative, CD68 – positive in the histiocytes. (Figures 9 and 10)

Based on the morphology and immunohistochemistry, a diagnosis of ALK-positive Anaplastic large cell lymphoma was made.

Anaplastic Large Cell Lymphoma (ALCL) is a group of mature T-cell lymphomas. ALCL commonly occurs in the lymph node (90%). ALCL is more common in

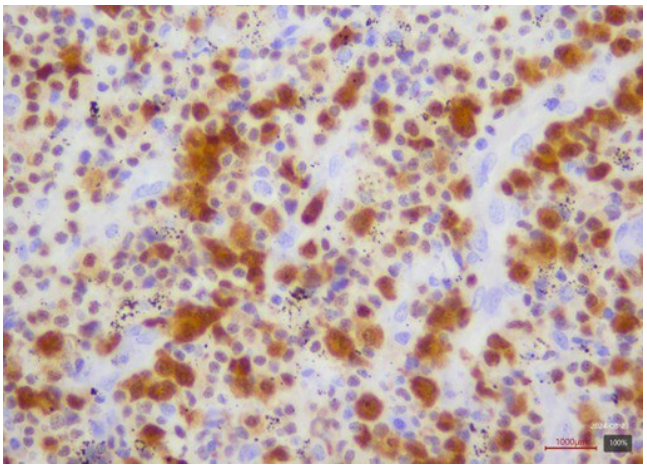

Figure 9. Case no. 6 (2576/24)- Immunohistochemical staining for CD 30 (positive).

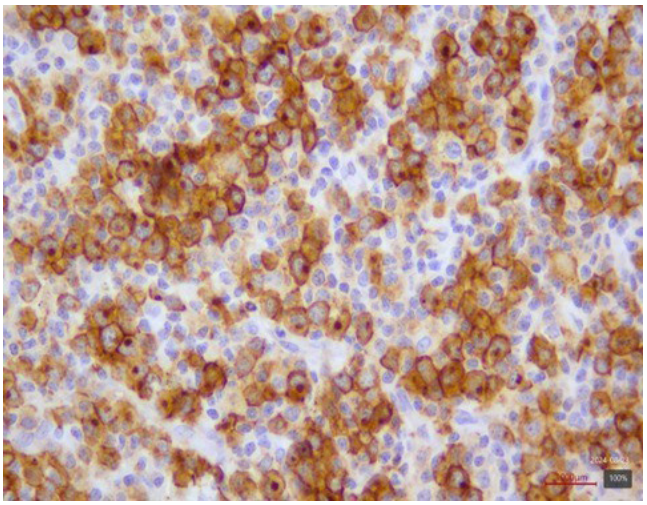

Figure 10. Caseno.6(2576/24)-Immunohistochemical staining for ALK (positive).

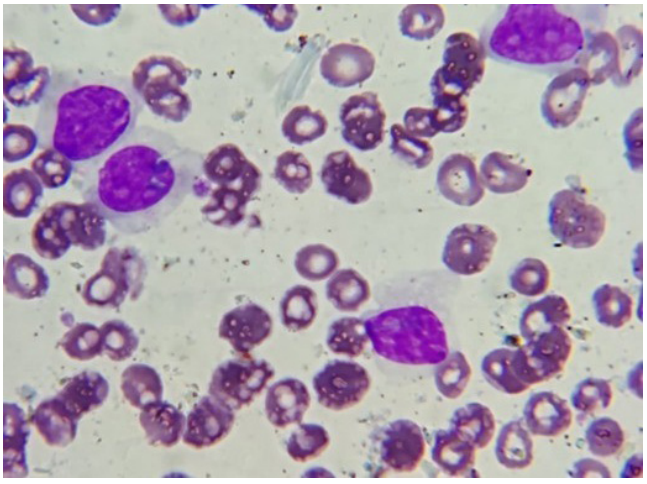

Figure 11. Case no. 7 showing atypical lymphoid cells in peripheral blood smear (Leishman stain)(40X).

the pediatric age group. Three entities are described – ALK-positive ALCL, ALK-negative ALCL and breast implant-associated ALCL. Morphological spectrum of ALCL is broad and it includes small cell variant, lymphohistiocytic variant, monomorphic variant, Hodgkin's pattern, neutrophil–rich background and sarcomatoid appearance. The differential diagnoses are metastatic carcinoma, Hodgkin lymphoma and plasmablastic lymphoma[11].

Case no. 7

A 42-year-old female presented with complaints of abdominal pain and loose stools for the past month and fever for one week. On examination, massive splenomegaly was seen.

Complete blood count – WBC -12.8*103, RBC – 2.55*106, Haemoglobin - 6.8g/dL, HCT – 22.3, MCV – 87.5, MCH – 26.7, MCHC – 30.5, PLT – 57000.

Peripheral smear examination – White blood cells show a mild increase in count, with predominant cells being atypical lymphoid cells, constituting 72%. The cells are medium-sized sized having a moderate amount of pale cytoplasm with a central round nucleus, clumped chromatin and one to two inconspicuous nucleoli. Red blood cells show mild anisopoikilocytosis. They are microcytic hypochromic cells, admixed with normocytic normochromic cells, few pencil-shaped cells. Platelets – reduced. Impression was given as Microcytic hypochromic anaemia, Mild Leucocytosis with lymphocytosis and thrombocytopenia. In view of the presence of many atypical lymphoid cells with blastoid morphology, bone marrow aspiration study, trephine biopsy and flow cytometry are suggested. (Figures 11 and 12)

Bone marrow aspiration was done, and smears studied are cellular with myeloid myeloid-erythroid ratio of 1:1.7. Erythroid series is active and shows hyperplasia with micronormoblastic and normoblastic maturation. A few binucleate and budding forms are seen, constituting less than 10%. The myeloid series shows a normal pattern of maturation. A few atypical lymphoid cells are seen, constituting 6% which are medium to large-sized sized having a moderate amount of cytoplasm, round nuclei with clumped chromatin and one to two distinct nucleoli. Megakaryocytes are adequate and normal in morphology. Impression was given as Erythropoiesis – Hyperplasia with micronormoblastic and normoblastic morphology. Myelopoiesis – Few atypical lymphoid cells (6%). Megakaryopoiesis -adequate. Flow cytometry for further evaluation was suggested. (Figure 13)

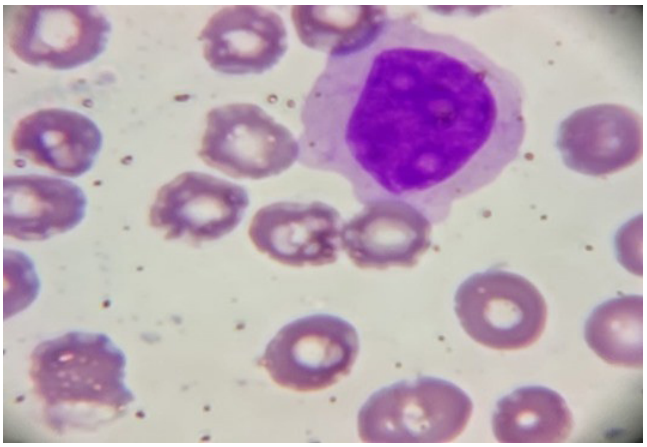

Figure 12. Case no. 7 showing atypical lymphoid cells with 3 nucleoli in peripheral blood smear (Leishman stain) (100X).

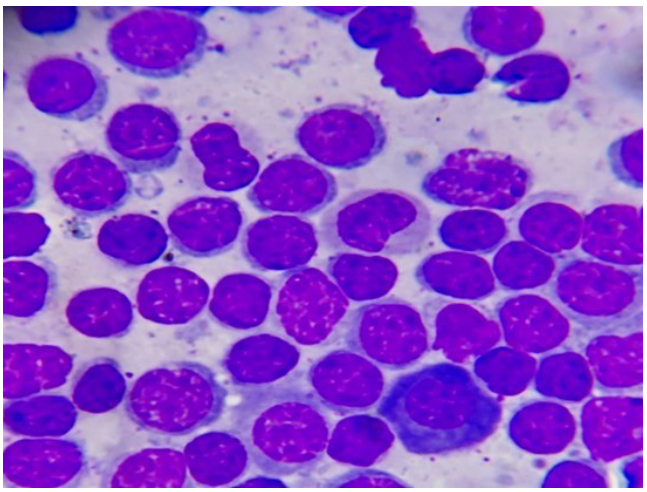

Figure 13. Case no. 7 showing a few atypical lymphoid cells in bone marrow aspirate (Leishman stain) (100X).

Trephine biopsy study showed interstitial infiltrates of a monotonous population of small lymphoid cells. Suggestive of Lymphoma infiltration. Reticulin stain showed Grade 3 marrow fibrosis (MF-3). Flow cytometric analysis of peripheral blood –

CD20 showed bright expression,

CD19, FMC-7, KAPPA, CD11c, CD45 showed moderate expression and

CD5, CD10, CD43, CD38, CD103, CD25, CD123, CD7, CD3, CD4, CD8, CD23, CD200, CD56 and

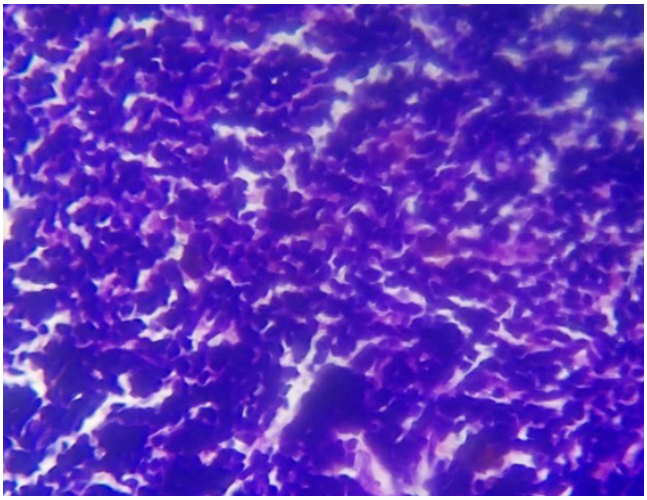

Figure 14. Case no. 7 (827/25) Small lymphoid cells in spleen (H and E) (40X).

LAMBDA showed a negative expression.

The possibilities considered are i) Splenic Marginal zone lymphoma

ii) Splenic B-cell lymphoma/leukaemia with prominent nucleoli

Spleen biopsy shows few lymphoid follicles with occasional follicles showing a central arteriole; the entire follicle shows sheets of small lymphocytes. The interfollicular zone shows small lymphoid cells and occasional plasma cells. No large atypical cells are seen. Impression – Correlating with the flow cytometry findings, features are suggestive of Small B-cell lymphoma, possibly marginal zone lymphoma. (Figure 14)

Marginal Zone Lymphoma is an indolent B-cell lymphoma, and it accounts for around 1–2% of all lymphomas. The median age at diagnosis is around 65 years. Almost all patients have splenomegaly with some degree of bone marrow and peripheral blood involvement. A precise diagnosis requires careful integration of clinical findings with the morphological, immunophenotypic and molecular features of bone marrow and peripheral blood involvement[12].

6. Summary and Conclusion

Most of the extra nodal Non-Hodgkin lymphomas confer a worse prognosis than their nodal counterpart. Plasmablastic lymphoma involving the eyelid and primary CNS lymphoma patients in this study succumbed to death soon after diagnosis. So early diagnosis and treatment are essential. Histopathological diagnosis plays a vital role in identifying these tumours in rare sites.

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