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An Unusual Culprit Behind Low Back Pain

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Abstract: ***Lymphomas are characterized by the aberrant and excessive proliferation of lymphoid cells. They are categorized into Hodgkin and Non-Hodgkin Lymphomas. While lymphomas frequently exhibit nodal and extranodal involvement, with metastasis to bone being common place, primary origins in bone are relatively rare. Primary bone lymphomas (PBL) result in osteolytic lesions or bone destruction, and patients typically present with non-specific localized symptoms. Nevertheless, a subset of cases may manifest with systemic B symptoms.***

We present a case involving a 52-year-old woman who experienced persistent lower back pain for one year. Upon further evaluation, MRI and PET/CT scans revealed multiple skeletal lesions, with increased density observed at the L5-S1 level and the right femur, suspected to be metastatic deposits. Based on the findings from a bone marrow biopsy and immunohistochemistry (IHC) analysis, the diagnosis was established as Primary Bone Lymphoma—specifically, Non-Hodgkin Lymphoma, Diffuse Large B Cell Lymphoma. Our patient was treated with targeted chemotherapy, and subsequent follow-up demonstrated a favorable response.

Abbreviations: PLB - Primary Bone Lymphoma, DLBCL - Diffuse Large B Cell Lymphoma, IHC - Immuno-histochemistry, MRI - Magnetic Resonance Imaging, PET/ CT - Positron Emmission Tomography/ Computed Tomography, ^{18}F-FDG - 18 FluoroDeoxyGlucose, CA - Cancer Antigen, CEA - Carcinoembryogenic Antigen, BCL2/ BCL6 - B-Cell Lymphoma 2/6 Protein, CD - Cluster of Differentiation, CARD11 - Caspase Recruitment Domain Containing Protein 11, MYD88 - Myeloid Differentiation primary response gene 88, ALK - Anaplastic Lymphoma Kinase, FISH - Fluorescence In Situ Hybridisation, R-CHOP - Rituximab with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, IPI - International Prognostic Index, ECOG - Eastern Cooperative Oncology Group.

I. INTRODUCTION

According to estimates, primary bone lymphoma (PBL) constitutes approximately 7% of all malignant bone tumors, 5% of all extra-nodal lymphomas and less than 1% of all adult non-Hodgkin lymphomas[1] (Table-1). Over the years, the definition of primary bone lymphoma has evolved. The World Health Organization (WHO) categorizes PBL as either a solitary osseous lesion devoid of regional lymph node

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involvement or as a neoplasm manifesting in multiple osseous sites without concurrent visceral or lymph node disease.

The International Extra-nodal Lymphoma Study Group (the IELSG 14 study)[2] also delineates similar lesions of distinct bone origin as primary bone lymphomas, which may present as either a single bony lesion or as "multifocal osseous lymphoma" or "polyostotic lymphoma." The majority of patients diagnosed with PBL are over the age of 45 with a male-to-female ratio of 1.8:1.2[3]. The femur is the most frequently affected site, accounting for approximately 50% of cases, with tumor infiltration predominantly along the shaft. The pelvis ranks as the second most commonly involved site, comprising around 20% of cases, while other affected locations include the spine, ribs, mandible, scapula, and proximal phalanx of the thumb.[4]

II. CASE HISTORY

A 52-year-old woman, with a marriage spanning 32 years and the responsibility of raising two children, presented to the outpatient department with persistent lower back pain that had not alleviated over the past year. She was subjected to a comprehensive evaluation. Her hemogram and peripheral blood smear yielded normal results. Biochemical parameters fell within acceptable limits, and Lactate Dehydrogenase was recorded as normal (178 U/L). Serological mucin markers, including CA 15-3, CA 125, and CEA, were within the normal range, with the exception of a mild elevation in CA 19-9 (43 U/ml). The patient underwent an array of imaging studies for further assessment. The work-up for Multiple Myeloma returned negative results. A mammography was conducted, revealing findings consistent with her age. MRI of the cervical spine reveals T1 hypo-intense and T2 hyper-intense lesions within the bone marrow at the C2, C3, and D3 vertebral bodies, suggestive of metastatic deposits. The MRI of the lumbosacral spine demonstrated T1 hypo-intense and T2 hyper-intense lesions within the bone marrow at the L1, L2, L5, and S1 vertebral bodies. Notably, marrow edema was observed in the sacral and iliac regions of the bilateral sacroiliac joints. An ill-defined soft tissue lesion was identified in the right para-vertebral region at the L5-S1 level, measuring 28x30 mm, exhibiting STIR hyper-intensity along the neurovascular bundles of the right L5 and S1 levels, further indicative of metastatic deposits.

PET/CT utilizing 18F-FDG (with radio tracer uptake in the mediastinal blood pool, SUV max - 1.8, and normal liver parenchyma, SUV max - 3.2) suggest significant presacral and multiple skeletal deposits, including those in the femur. Numerous FDG-avid skeletal lesions were present, involving the cervico-dorso-lumbar spine, bilateral ribs, bilateral scapulae, sternum, head of the left humerus, multiple sites in the bony pelvis, bilateral acetabulae and femur. The apex of metabolic activity was noted in the head of the right femur (SUV max 10.0) (Fig-2). Additionally, an FDG-avid soft tissue density deposit was identified in the presacral region measuring 1.5APx1.7TRx2.3CC (SUV max 8.1) (SV-1 level), situated posterior to the psoas major muscle (Fig-1). Imaging also indicated a mildly FDG-avid left level Vb cervical lymph node (10mm in MSAD, SUV max 2.4) and several other mildly FDG-avid sub-centimetric bilateral level II cervical lymph nodes. A number of mildly FDG-avid level I, II, and III axillary lymph nodes were observed, with the highest metabolic uptake recorded at 1.5APx0.7TRx1.0CC (SUV max 1.8) within the level II station.

Following the imaging, with a suspicion of malignancy, a bone marrow biopsy was performed. The biopsy from the L5-S1 level revealed a core exhibiting 11-12 inter-trabecular spaces and hyper-cellular marrow for age (approximately 90% cellularity) (Fig-3). The marrow was infiltrated by lymphoid cells arranged in a nodular pattern. These lymphoid cells were polymorphic, with the majority being medium to large-sized, round to oval, characterized by an increased nuclear-to-cytoplasmic ratio, irregular nuclear membranes, and some displaying cleaved nuclei and vesicular chromatin (Fig-4). Focal areas demonstrated normal hematopoiesis. Immunohistochemical analysis revealed positive staining for CD20, BCL2, and CD10 in the nodular infiltrate of atypical lymphoid cells (Fig-5 to 7), while being negative for CD5, BCL6, and Cyclin D1. CD3 positivity was noted in interspersed T-lymphocytes (Fig-8). The final opinion offered was Primary Bone Marrow Lymphoma - Non-Hodgkin Lymphoma, specifically Diffuse Large B-Cell Lymphoma (GCB), as no other significant nodal deposits were identified. Subsequently, the patient underwent six cycles of chemotherapy utilizing the R-CHOP regimen. Follow-up imaging reveals chemotherapy-induced diffuse marrow hyperplasia, with no significantly enlarged FDG-avid lymph nodes and a resolution of previous skeletal deposits. The patient is currently in good health. Her IPI score stands at 1[5,22] (Table 2), and her ECOG performance status is 1[6] (Table 3).

III. DISCUSSION

PBL was first described by Oberling[7] in 1928 and is considered a very rare condition. The etiology of PBL remains largely obscure; however, it is distinguished by its propensity to affect any segment of the skeletal system. The femur is predominantly implicated, accounting for approximately 50% of cases. Metastatic involvement of lymph nodes and distant bone marrow occurs in roughly 28% and 35% of instances, respectively. Spinal cord compression represents the most formidable complication associated with this malignancy, impacting 16% of patients. Osteolysis and consequent hypercalcemia are additional significant complications observed in approximately 5–10% of cases[8]. Timely recognition of these medical emergencies is imperative to avert further complications. PBLs may be erroneously diagnosed as rheumatic diseases, chronic osteomyelitis, metastatic bone neoplasms, or other primary osseous tumors such as osteosarcoma; it is imperative that these conditions are meticulously excluded prior to establishing a definitive diagnosis of PBL. Other differential diagnoses for PBL include primary bone sarcoma, leukemic infiltrate, small blue round cell tumors (including Ewing Sarcoma/ Primitive Neuroectodermal Tumor, Rhabdomyosarcoma, Metastatic Neuroblastoma, and Small-cell Osteosarcoma), Metastatic sarcomas & Mesenchymal Chondrosarcoma[9].

ISSN: 2394-4404

The definition of primary bone lymphoma (PBL) is elucidated by the following criteria[10]:

- ✓ The principal locus of tumorigenesis resides within the bone marrow, absence of any adjunct sites indicative of the lesion upon physical examination or imaging studies;
- ✓ No evidence of lymphoma at any alternate site discerned six months subsequent to the diagnosis of primary B-cell lymphoma;
- ✓ The diagnosis must be substantiated through histopathological examination and immunohistochemistry; and
- ✓ Malignant lymphomas, with the exception of primary bone lymphoma (PBL) and secondary lymphoma of the bone, must be unequivocally excluded.

The staging systems for PBL are:

- Lugano Classification System[11]
- Ann Arbor staging system

ANN ARBOR STAGING SYSTEM[12]

- ✓ Stage I, characterized by a solitary lesion within the osseous tissue with or without soft tissue infiltration;
- ✓ Stage II, characterized by the presence of more than two lesions on one side of the diaphragm, or a solitary lesion within the bone accompanied by soft-tissue infiltration;
- ✓ Stage III, characterized by lesions present on both sides of the diaphragm; and
- ✓ Stage IV, characterized by the infiltration of the central or peripheral nervous system, as well as the bone marrow, as ascertained through staging biopsy conducted at various intervals.

A study conducted by *Heyning et al.*[13] classified 46% of patients with primary lymphoblastic lymphoma (PLB) as stage I, 16% as stage II, another 16% as stage IV, and 20% as an indeterminate. Non-Hodgkin lymphoma (NHL) constitutes the predominant form of PLB, with the most prevalent subtype originating from B-cells, whereas primary Hodgkin lymphoma of the bone remains an infrequent occurrence.[1] (Table-1).

The sensitivity, specificity, and accuracy rates for the staging of extra-nodal lymphomas utilizing PET-CT have been documented at 97%, 100%, and 98%, respectively, in contrast to the rates of 87%, 85%, and 84% observed with conventional CT imaging.[14] According to the Kiel classification[16], 45-78% of primary non-Hodgkin lymphoma (NHL) of the bone are characterized as centroblastic and multilobulated. BCL-6 exhibited positivity in 30% of cases, while pronounced p53 protein expression was detected in 11 out of 20 (55%) instances. Upon morphological examination, neoplastic cells were notably large and exhibit characteristics consistent with follicle center or centroblastic cell types. *Heyning et al.*[12] also observed diminished survival durations in patients with the immunoblastic subtype in comparison to those with the centroblastic mono/polymorphic or centroblastic multilobulated subtypes. Flow cytometry[18,19] reveals immunoreactivity for B-cell markers including CD20, CD21, CD45, and CD79a, accompanied by variable immunoreactivity for CD75 and CD10. T-cell markers are typically negative, with only a few cases demonstrating focal CD3 positivity. The extant data regarding primary bone T-cell lymphomas remains insufficient, with the majority of reported instances being Anaplastic large-cell lymphoma (CD3 +; CD43+; CD30+), frequently associated with t(2;5)(p23;q35) and ALK-1 expression[20]. In primary bone diffuse large B-cell lymphoma (DLBCL), BCL2 translocation was identified in approximately 20% of cases, BCL6 translocation in 14%, and MYC translocation in 10%. High-grade B-cell lymphomas are characterized by the presence of MYC, in conjunction with BCL2 and/or BCL6 rearrangements, referred to as double-hit lymphomas. A study conducted by *Lima et al.* meticulously examines the gene expression signatures associated with primary bone lymphoma (PBL) and reveals that 6 out of 8 cases displayed BCL2 rearrangement, while an additional 5 out of 17 cases were identified as harboring MYC rearrangements[15]. Furthermore, a clonal B-cell process, as evidenced by immunoglobulin heavy chain gene rearrangement, was observed in the majority of cases (13 out of 18; 72%)[17]. The implementation of Triple (BCL2/BCL6/MYC) FISH in DLBCL signifies a remarkable progression in diagnostic methodologies.

Recently, the genomic landscape of diffuse large B-cell lymphoma (DLBCL) has been meticulously examined through extensive next-generation sequencing investigations conducted on substantial cohorts of B-cell lymphomas. These studies have elucidated the prevalence of pivotal driver mutations in genes such as MYD88, CD79A/CD79B, CARD11, and TP53, which are correlated with a dismal prognosis and a propensity for resistance to therapeutic interventions.[21].

Currently, a diverse array of treatment modalities exists for PBL, encompassing chemotherapy, localized radiation therapy, and surgical intervention. In light of the burgeoning advancements in novel systemic therapies, further investigation is imperative to ascertain treatment regimens that will enhance progression-free and overall survival rates for patients afflicted by PBL.

The conventionally employed regimen comprises Rituximab in conjunction with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R–CHOP)[23]. For patients exhibiting hypersensitivity to anthracyclines, the alternative regimen is R-COEP (Rituximab with Cyclophosphamide, Vincristine, Etoposide, and Prednisone)[24]. A novel anti-CD20 monoclonal antibody, Obinutuzumab, has been utilized for the first time alongside conventional chemotherapy to mitigate the adverse effects associated with Rituximab, including drug resistance, refractory/relapse phenomena, and disease progression.[25]

Unifocal bone disease serves as a favorable prognostic indicator in primary lymphoma of bone (PLB), while multifocal disease, soft-tissue infiltration, and elevated International Prognostic Index scores constitute significant adverse prognostic determinants. Additional favorable prognostic factors in PLB encompass early-stage disease, a younger demographic (specifically those under 60 years), diminished serum lactate dehydrogenase (LDH) levels, and an optimal Eastern Cooperative Oncology Group (ECOG) performance status.[26]

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IV. CONCLUSION

PLB, also known as Reticulum Cell Sarcoma, is an infrequent yet exceptionally responsive malignancy to chemotherapy among the various lymphomas. Consequently, prompt diagnosis and management significantly enhance therapeutic outcomes and progression-free survival for patients. The Eastern Cooperative Oncology Group (ECOG) performance status and the International Prognostic Index (IPI) score are pivotal for guiding treatment decisions and monitoring patient progress.

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We thank the patient and her family for the publication of this case report.

Classification	uPBL	mPBL	SBL
DLBCL, n (%)	37(80.4)	23(65.7)	23(50.0)
Follicular lymphoma, n (%)	4(8.7)	3(8.6)	9(19.6)
Small lymphocytic lymphoma, n (%)	1(2.2)	1(2.9)	0(0)
Marginal zone lymphoma, n (%)	1(2.2)	1(2.9)	2(4.3)
Not further subclassified[a], n (%)	1(2.2)	2(5.7)	1(2.2)
BLUI , n (%)	0	1(2.9)	0(0)
Classical Hodgkin lymphoma, n (%)	1(2.2)	0(0)	10(21.7)
T cell, n (%)	1(2.2)[b]	4(11.4)[c]	1(2.2)[d]
Total, n (%)	46	35	46

Abbreviations uPBL: primary bone lymphoma with unifocal bone disease; mPBL: primary bone lymphoma with multifocal bone disease; SBL: secondary bone lymphoma; DLBCL: diffuse large B-cell lymphoma; Large B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymhoma: BLUI; ALCL: anaplastic large T-cell lymphoma; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified.
[a]Low-grade, small B-cell lymphoma no further information for subclassification.
[b]ALCL(n = 1).
[c]ALCL (n = 2), T-lymphoblastic lymphoma (n = 1), and PTCL, NOS (n = 1).
[d]ALCL (n = 1).

Table 1: Histopathological subtypes in Bone Lymphoma[1]

Risk Factor	0 Point	1 Point
IPI		
Age	≤60 years	>60 years
Ann Arbor stage	I or II	III or IV
Serum LDH level	Normal	Above normal
Number of extranodal sites of involvement	≤1	>1
ECOG performance status	0–1	≥2
aaIPI (≤60 years or >60 years)		
Ann Arbor stage	I or II	III or IV
Serum LDH level	Normal	Above normal
ECOG performance status	≤1	>1

Table 2: The International Prognostic Index (IPI) and age-adjusted IPI for Non-Hodgkin's Lymphoma[5]

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*Table 3: *These scales and criteria are employed by medical professionals and researchers to evaluate the progression of a patient's illness, analyze the impact of the disease on the patient's daily living capabilities, and ascertain suitable treatment options and prognostic outcomes. They are included here for the convenience of healthcare practitioners to access[6]*

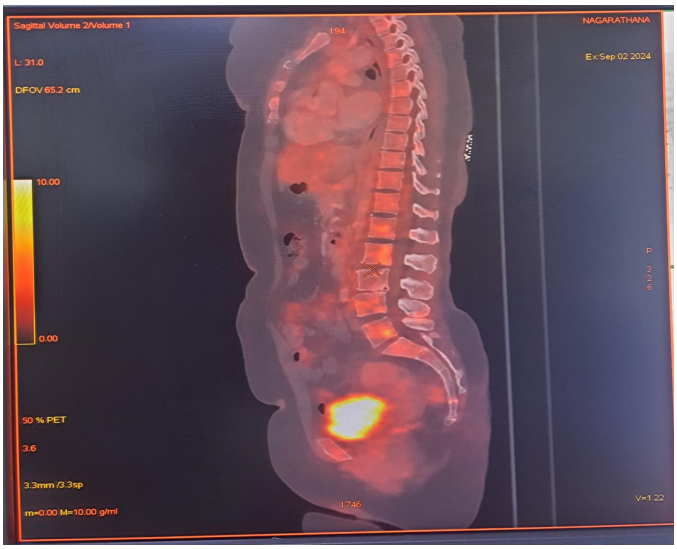

Figure 1: PET-CT image showing multiple FDG avid skeletal lesions involving cervico-dorso-lumbar spine

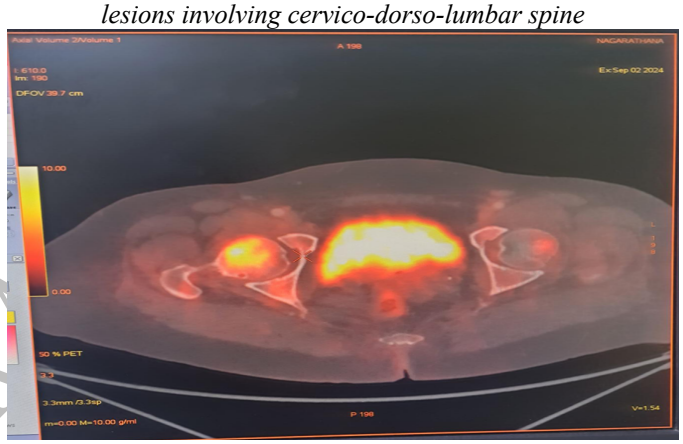

Figure 2: PET-CT image showing FDG avid skeletal lesions involving bilateral acetabulae & femur

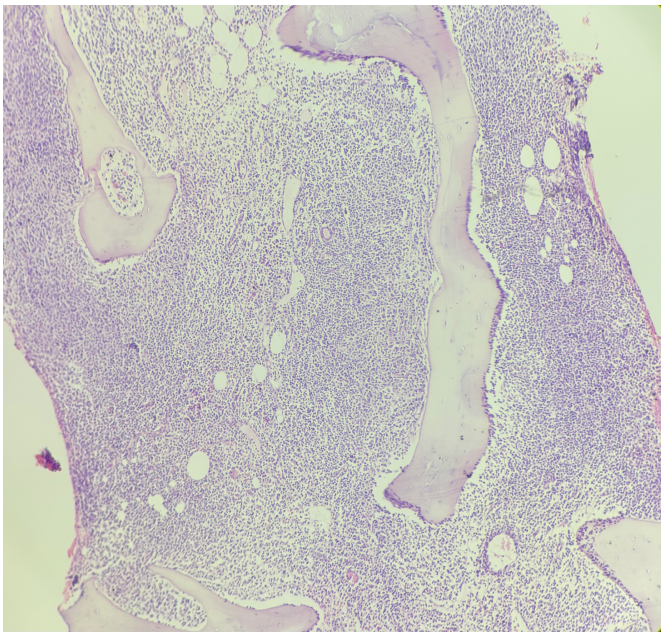

Figure 3: Scanner view of Bone marrow biopsy – Adequate and Hyper cellular marrow for age with nodular pattern of infiltration by lymphoid cells

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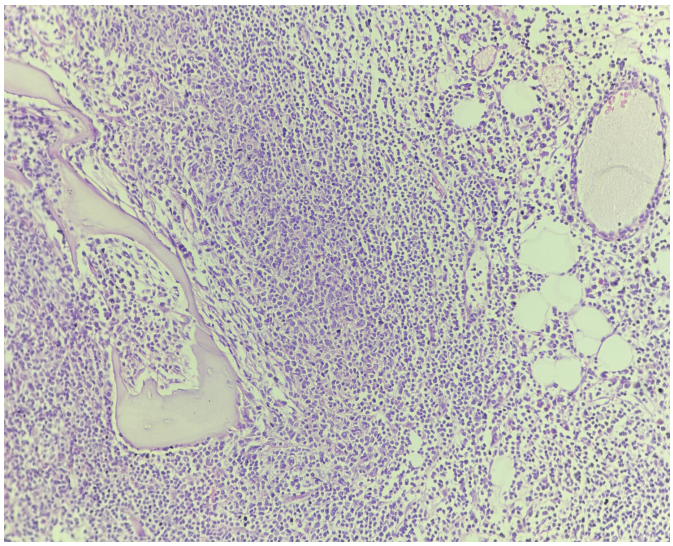

Figure 4: 40x view of bone marrow biopsy (H&E): Nodular pattern of infiltration by lymphoid cells

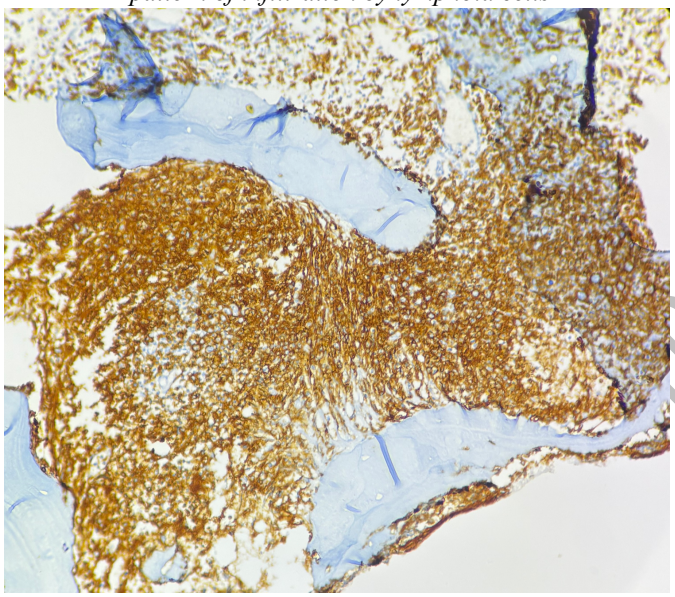

Figure 5: IHC - CD20: Positive in B- lymphocytes (nodules)

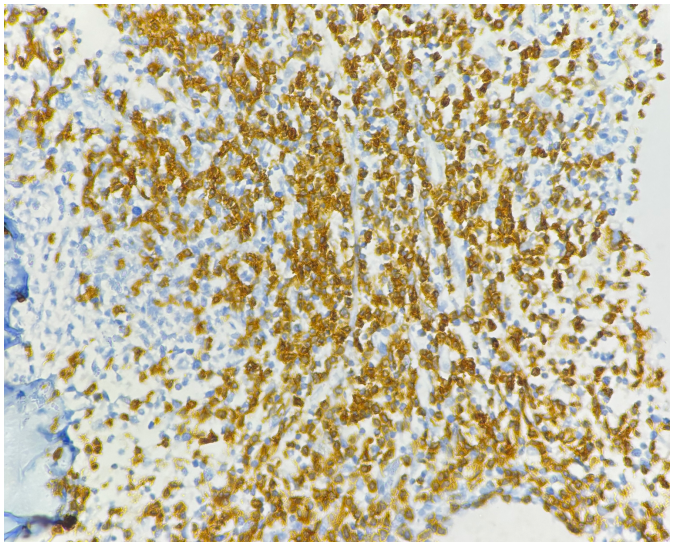

Figure 6: IHC - BCL2: Positive in lymphoid population (nodules)

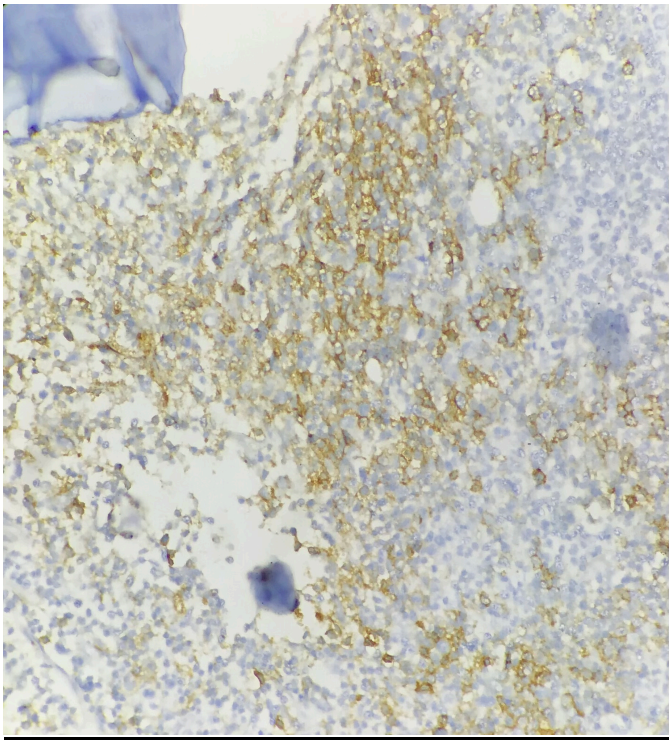

Figure 7: IHC - CD10: Positive in lymphoid population (nodules)

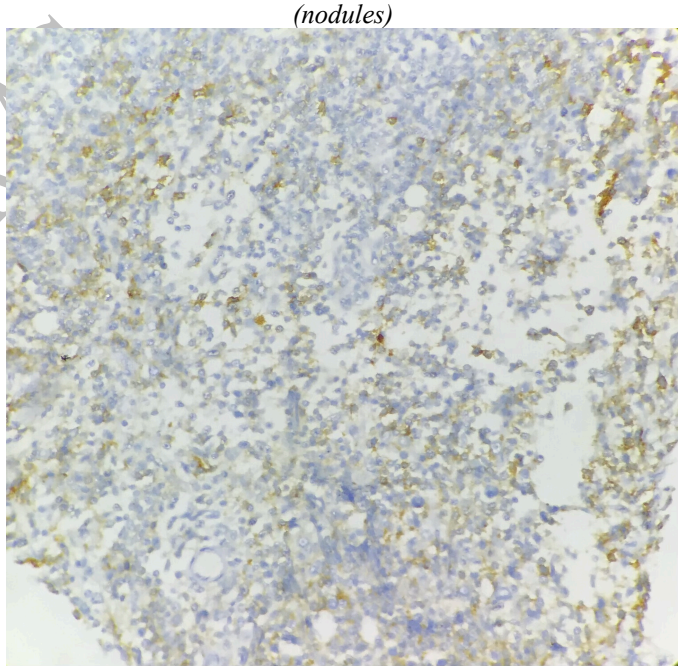

Figure 8: IHC - CD3: Negative in atypical lymphoid population, positive in interspersed T-lymphocytes

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