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BEYOND THE NODES: HIDDEN LYMPHOID STRONGHOLDS — A CASE SERIES OF PRIMARY EXTRANODAL LYMPHOMAS

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ABSTRACT

Background: Extranodal lymphomas represent a diagnostically challenging and clinically diverse group of lymphoid neoplasms that arise outside the conventional lymph node chain. Primary extranodal sites — including the central nervous system (CNS), testis, breast, and omentum — are rarely affected, and their accurate recognition requires integration of clinical, radiological, histomorphological, and immunohistochemical data.

Methods: We report a retrospective case series of four patients diagnosed with primary extranodal lymphoma at SRM Medical College Hospital and Research Centre, Chengalpattu, India (2024–2025). Specimens were processed by standard formalin-fixed paraffin-embedded technique; histopathological examination and immunohistochemistry (IHC) were performed in all cases.

Results: The series includes: (1) a 60-year-old male with primary testicular diffuse large B-cell lymphoma (DLBCL); (2) a 58-year-old male with primary CNS lymphoma of B-cell origin with high Ki-67 proliferative index; (3) a 56-year-old female with primary breast non-Hodgkin lymphoma (NHL) of B-cell type; and (4) a 45-year-old female with follicular lymphoma (FL) presenting incidentally as a primary omental mass. In all cases, IHC confirmed B-cell lineage (CD20-positive, CD3-negative). The omental FL was further classified as grade 1, stage II, with positivity for CD10, BCL2, and BCL6 and a low Ki-67 of 8–10%.

Conclusion: This case series highlights the morphological spectrum and diagnostic challenges of primary extranodal lymphomas across rare sites. Comprehensive histopathological and immunohistochemical evaluation is indispensable for accurate subtyping, prognostication, and treatment planning.

KEYWORDS: extranodal lymphoma; diffuse large B-cell lymphoma; CNS lymphoma; testicular lymphoma; breast lymphoma; follicular lymphoma; omental mass; immunohistochemistry; non-Hodgkin lymphoma

1. INTRODUCTION

Lymphomas are broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with NHL accounting for approximately 90% of all cases.1 NHL arises from B-cell precursors, mature B cells, T-cell precursors, or mature T cells; the most prevalent subtypes in mature B cells include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), followed by mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL).1

While lymphomas most commonly affect lymph nodes — particularly cervical, axillary, and inguinal chains — a significant subset arises in extranodal sites. The gastrointestinal (GI) tract is the most commonly involved extranodal location, accounting for 30–40% of extranodal lymphomas and 4–20% of all NHL cases.2,3 Other well-recognised extranodal sites include the skin, bone, brain, testis, and breast.4 Primary CNS lymphoma (PCNSL) has an incidence of approximately 0.26 per 100,000; primary testicular lymphoma (PTL) occurs at an annual incidence of 0.4–0.5 per 100,000; and primary breast lymphoma accounts for only 0.1–0.5% of all breast malignancies.5,6,7

Follicular lymphoma is the second most common NHL subtype in the Western world, though it constitutes only 7.2% of NHL in India.8 It is a slowly progressive B-cell malignancy originating from germinal-centre B cells, characterised by a follicular growth pattern and, typically, an indolent clinical course.9 Primary omental involvement is exceedingly rare; the omentum, a peritoneal fold composed of fibrofatty tissue, lacks native lymphoid tissue, making primary lymphoma therein a notable diagnostic curiosity.10 Primary mesenteric tumours occur in fewer than 1 in 200,000 cases, with FL being the most prevalent type.10,11

Accurate diagnosis of extranodal lymphomas demands a multimodal approach integrating clinical presentation, imaging, histomorphology, IHC, and where appropriate, molecular and cytogenetic analyses.12 We present a case series of four patients with primary extranodal lymphoma at diverse rare sites, with the aim of highlighting their clinicopathological features, IHC profiles, diagnostic challenges, and outcomes.

2. MATERIALS AND METHODS

Study design: Retrospective case series.

Study period and setting: Cases were collected from SRM Medical College Hospital and Research Centre, SRMIST, Chengalpattu, India, over 2024–2025.

Sample size: Four cases of histologically confirmed primary extranodal lymphomas.

Specimen processing: All specimens were received in 10% neutral buffered formalin. Proper fixation, grossing, and tissue processing were performed according to standard protocols. Paraffin sections of 4 µm thickness were stained with haematoxylin and eosin (H&E) for histopathological examination. Additional 4 µm sections were taken for IHC after thorough H&E review.

Immunohistochemistry: IHC was performed using the standard avidin–biotin–peroxidase complex method. Antibody panels were tailored to each case and included CD3, CD20, CD45, CD10, BCL2, BCL6, BCL1 (cyclin D1), Ki-67, ER, PR, and synaptophysin, as indicated.

Ethical statement: The study was conducted in accordance with institutional ethical guidelines. Patient consent was obtained or waived as applicable for retrospective case reporting.

3. CASE PRESENTATIONS

3.1 Case 1: Primary Testicular Diffuse Large B-Cell Lymphoma

Clinical presentation: A 60-year-old male presented with progressive scrotal swelling of four months' duration. On examination, the right testis was not palpable separately from the mass, which measured approximately 6 × 3 cm.

Radiology: Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis demonstrated a mass replacing the right testis with extension along the spermatic cord. Inguinal orchidectomy was performed.

Fine-needle aspiration cytology (FNAC): Cytological smears showed cells with hyperchromatic nuclei, irregular nuclear membranes, marked anisonucleosis, prominent pleomorphism, and prominent nucleoli.

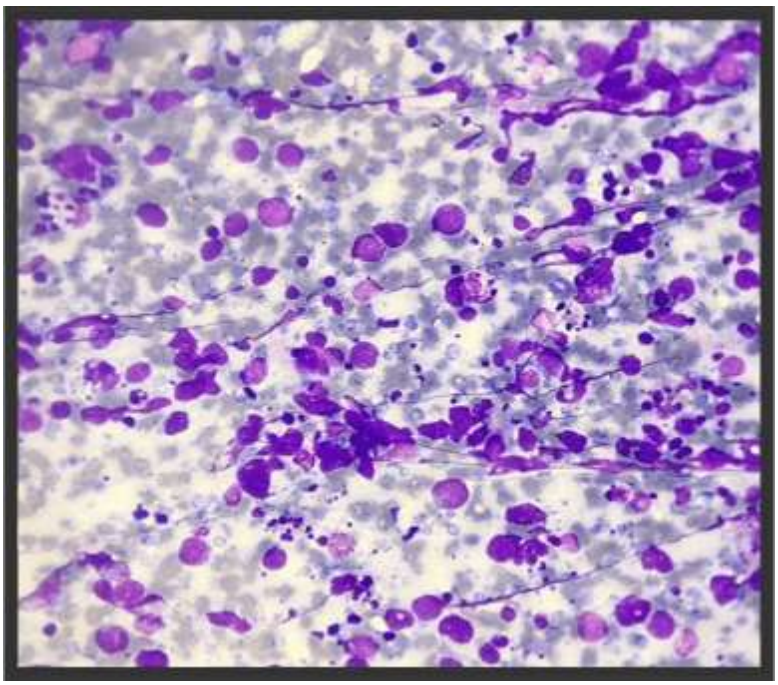

Figure 1:Cells have Hyperchromatic nuclei, Irregular nuclear membrane,Marked anisonucleosis, Marked pleomorphism, prominent nucleoli.

Gross pathology: The cut surface of the orchidectomy specimen showed a heterogeneous appearance with grey-white to grey-brown fibrotic areas.

Figure 2:Cut surface shows a heterogeneous appearance with grey white to grey brown fibrotic areas.

Microscopy: Histological sections revealed diffuse sheets of lymphoid cells obliterating the seminiferous tubules with intertubular spread and areas of necrosis. The cells were round to oval with irregular and multilobulated nuclei, fine to vesicular chromatin, prominent nucleoli, and scant to moderate eosinophilic cytoplasm — features consistent with large-cell lymphoma.

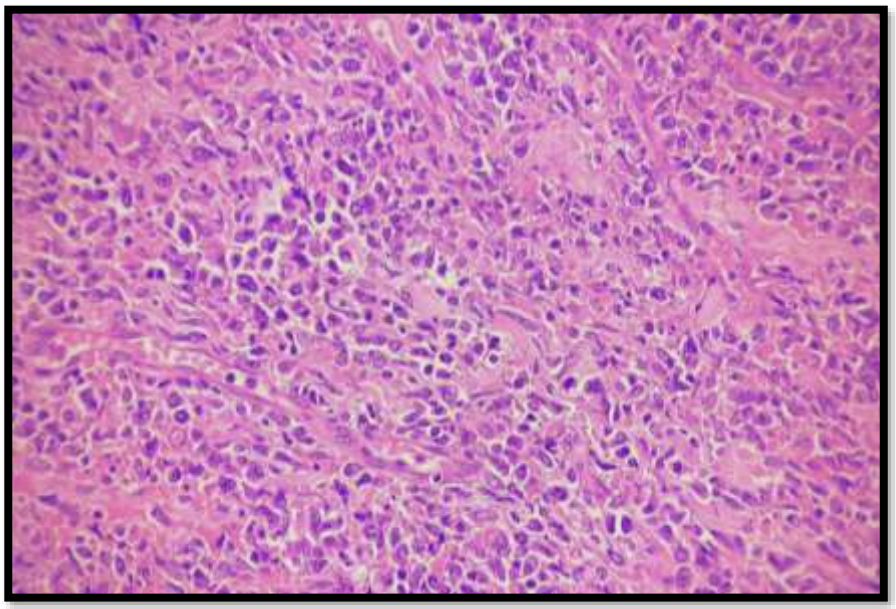

Figure 3: Histopathology(400x): Sections revealed diffuse sheets of lymphoid cells obliterating the seminiferous tubules

Immunohistochemistry: CD45 positive; CD20 diffusely positive; BCL2 positive; CD3 negative.

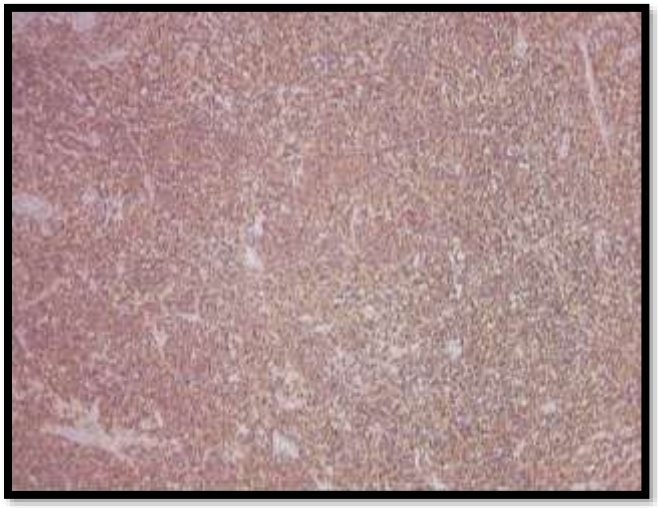

Figure 4: Immunohistochemistry(x100) CD 20 :Diffuse strong positivity in tumor cells

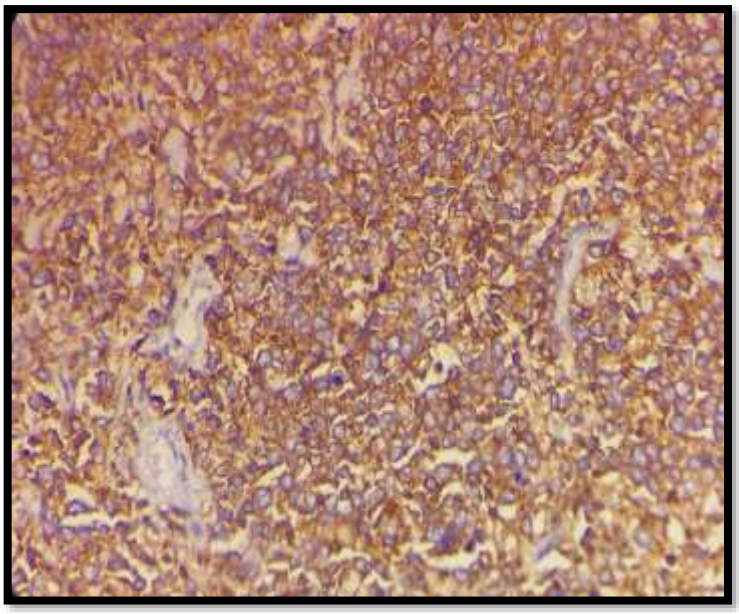

Figure 4: Immunohistochemistry:(x400): CD 45,Diffuse strong positivity in tumor cells

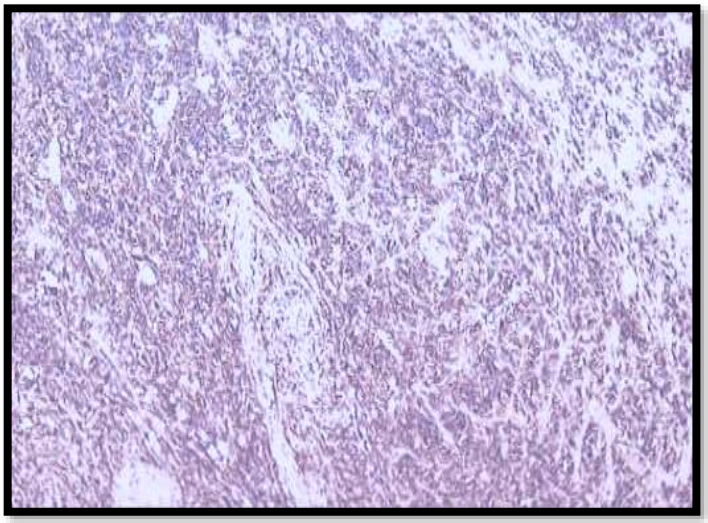

Figure 5: Immunohistochemisty:(x 400): Bcl 2, Positive in tumor cells

Final diagnosis: Diffuse Large B-Cell Lymphoma (DLBCL), primary testicular.
Primary testicular lymphoma (PTL) represents 1–9% of all testicular tumours and is the most common testicular malignancy in men over 60 years.5,6 It is an aggressive NHL, most frequently DLBCL, with a propensity for bilateral involvement and CNS relapse.13 Immune-privileged sites such as the testis are characterised by impaired immune surveillance, which may facilitate lymphomagenesis.7 Molecular testing for MYD88 and CD79B mutations is increasingly important for subtyping in testicular and CNS DLBCL.7

3.2 Case 2: Primary Central Nervous System Lymphoma

Clinical presentation: A 58-year-old male presented with a one-month history of headache and vomiting.
Radiology: CT and MRI of the brain demonstrated a space-occupying lesion (SOL) in the anterior wall of the third ventricle.
Microscopy: Sections showed benign glial tissue with infiltrating sheets of atypical lymphoid cells. The cells demonstrated scant cytoplasm with hyperchromatic nuclei and prominent nucleoli.

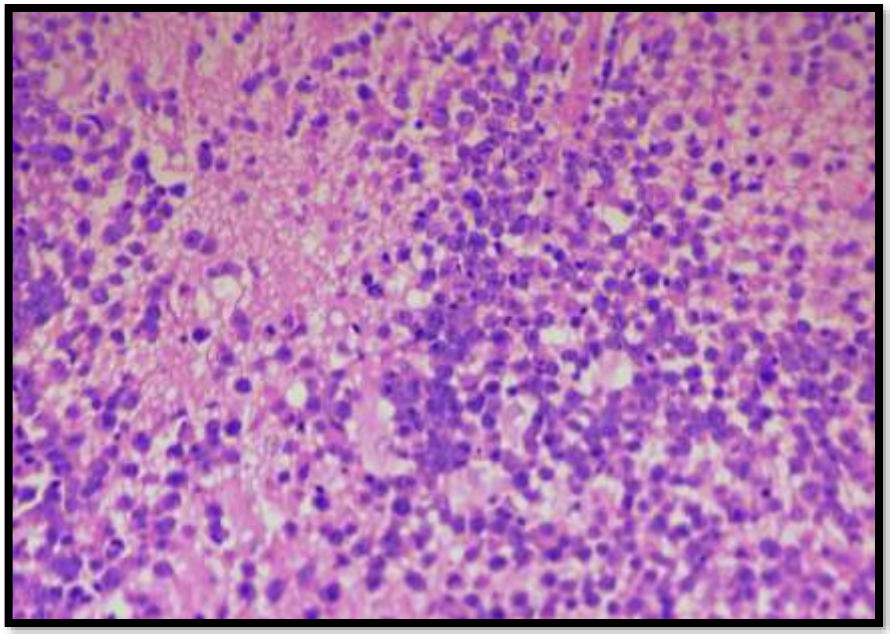

Figure 6: Histopathology (x400): Shows benign glial tissue with infiltrating sheets of atypical lymphoid cells.

Immunohistochemistry: CD45 positive; CD20 positive; CD3 negative; Ki-67 65–70%.

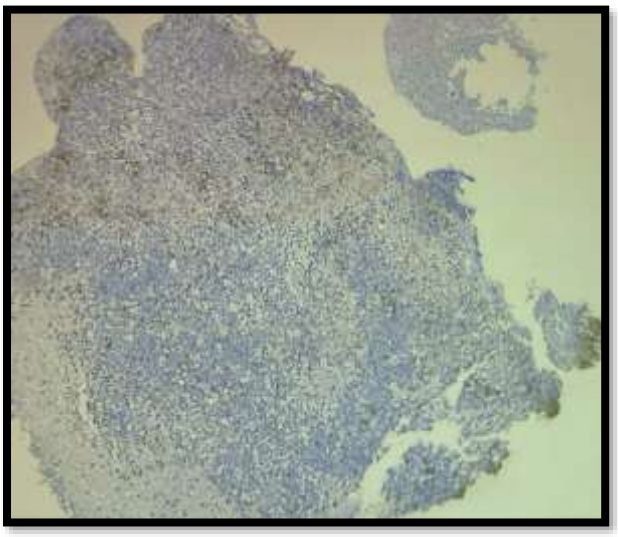

Figure 7: Immunohistochemistry(x400) : CD 3 : Negative in Tumor cells.

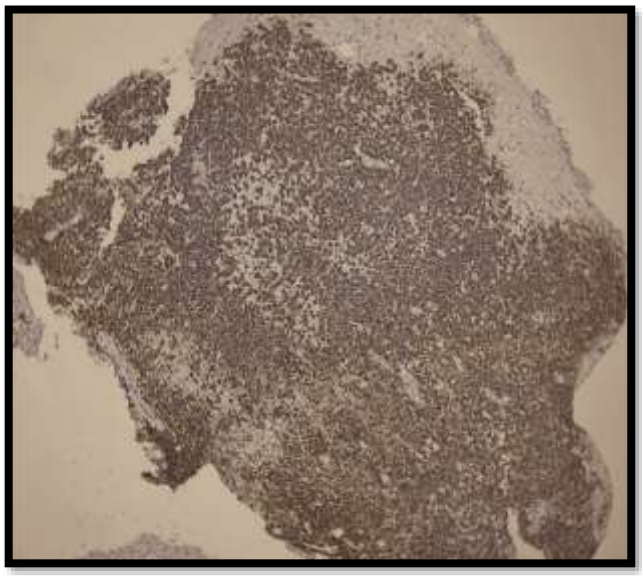

Figure 8: Immunohistochemistry (x100): CD 20:Positive in tumor cells

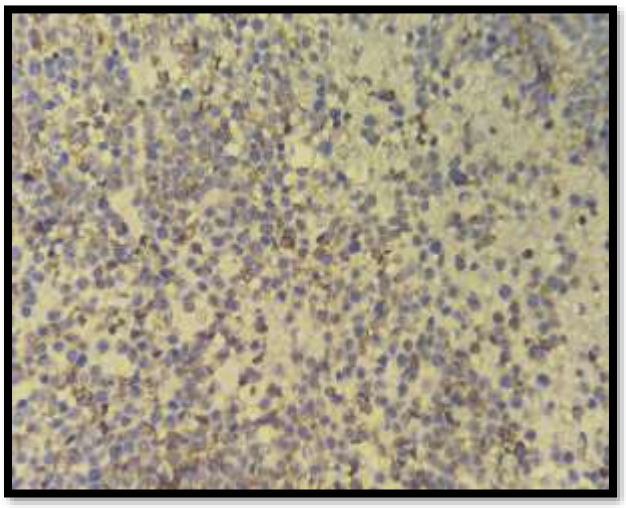

Figure 9: Immunohistochemistry (x 400) CD 45 : Positive in tumor cells

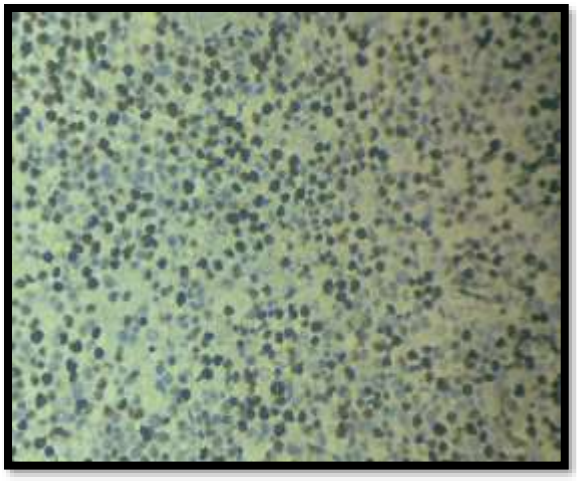

Figure 10: Immunohistochemistry: (x 400): Ki 67:65-70%

Final diagnosis: Non-Hodgkin Lymphoma, B-cell origin with high proliferative index- Primary CNS lymphoma
Primary CNS lymphoma (PCNSL) constitutes approximately 2–3% of all primary brain tumours and about 4–6% of all extranodal lymphomas.14 The vast majority (>90%) are DLBCL.15 PCNSL carries a poor prognosis compared to systemic DLBCL; the high Ki-67 index (65–70%) in this case reflects the aggressive proliferative biology typical of this entity.13,15 The aetiology remains largely unknown, though immune dysregulation — whether iatrogenic or secondary to conditions such as HIV — is a recognised predisposing factor.7

3.3 Case 3: Primary Breast Non-Hodgkin Lymphoma

Clinical presentation: A 45-year-old female presented with a breast swelling, for which a tru-cut biopsy was performed.
Microscopy: Histological sections showed small round blue cells with mildly pleomorphic, round to oval, hyperchromatic nuclei and scanty cytoplasm. No glandular or ductal structures were identified.

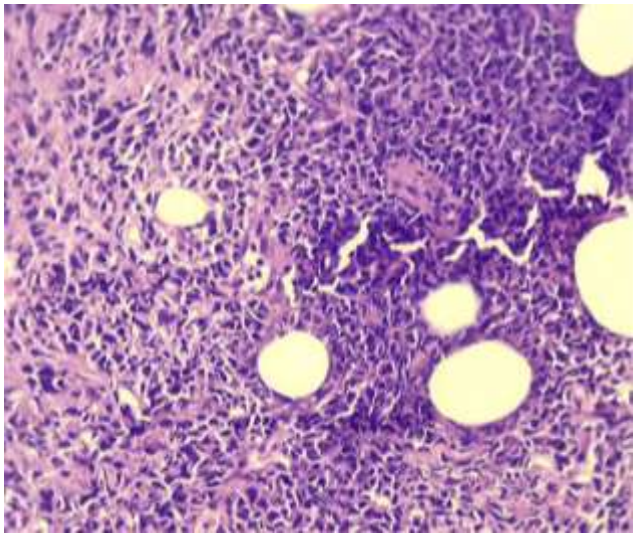

Figure 11: Histmorphology: (x 400): Small round blue cells with mildly pleomorphic , round to oval , hyperchromatic nuclei and scanty cytoplasm

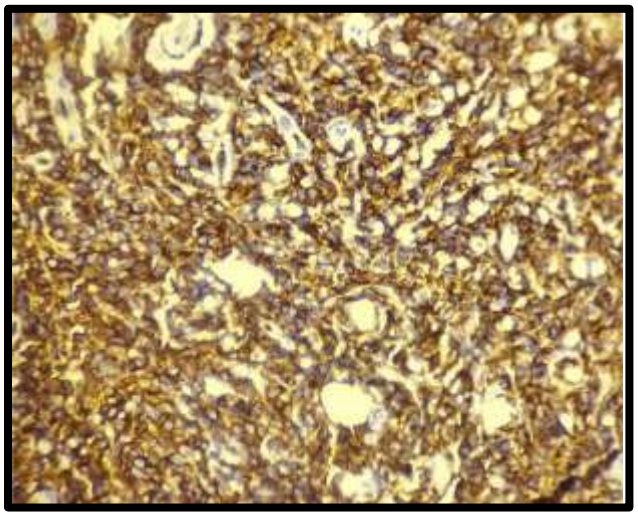

Figure 12:CD 45, CD 20 Positive in tumor cells

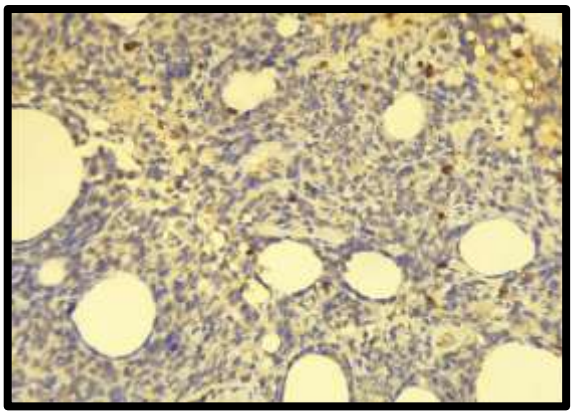

Figure 13:CD 3: Negative in tumor cells

Immunohistochemistry: CD45 positive; CD20 positive; CD3 negative; ER negative; PR negative; synaptophysin negative.
Final diagnosis: Non-Hodgkin Lymphoma, B-cell type, primary breast.
Primary breast lymphoma (PBL) is a rare entity, accounting for 0.1–0.5% of all breast malignancies and approximately 2% of extranodal lymphomas.7,16 The most common subtype is DLBCL, though marginal zone lymphoma and Burkitt

lymphoma are also reported.16 Accurate IHC exclusion of carcinoma (ER, PR, HER2) and neuroendocrine tumour (synaptophysin, chromogranin) is essential before confirming a lymphoid diagnosis in the breast.7

3.4 Case 4: Follicular Lymphoma as a Primary Omental Mass

Clinical presentation: A 40-year-old female presented with a three-month history of heavy menstrual bleeding .

Radiology: CECT of the abdomen showed a well-defined, soft-tissue density lesion in the mesentery.

Surgery: The patient was planned for total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH + BSO).

Gross pathology: The omental mass specimen seen with a nodule along with attached fatty tissue, whole measuring 9.3× 4 .5× 2 cm overall. The cut surface was grey-white , homogeneous, and firm.

Microscopy: Histological sections of the nodular lesion revealed sheets of lymphoid cells .Well-defined follicles composed of a monomorphic population of cleaved lymphocytes with scant cytoplasm, round nuclei (centrocytes) . The bilateral pelvic lymph nodes showed involvement by neoplastic lymphocytes.

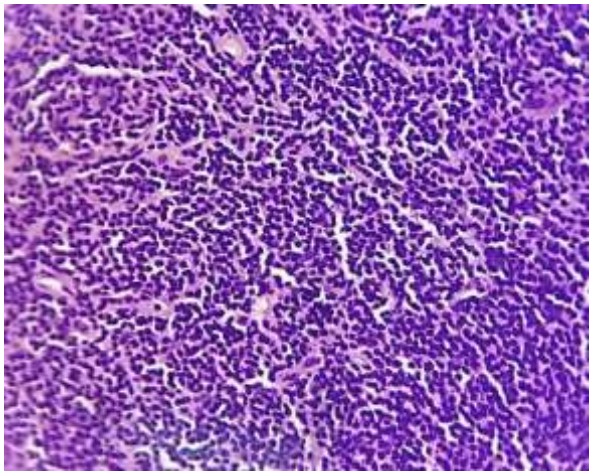

Figure 14: H and E (x40): Monomorphic population of small cleaved lymphocytes with round nuclei , dense chromatin , scant cytoplasm.

Immunohistochemistry: CD20 showed strong membranous positivity in neoplastic lymphocytes within poorly formed germinal-centre areas. CD3 showed strong membranous and cytoplasmic positivity in the interspersed T-lymphocytes within the parafollicular region. BCL2 demonstrated diffusely strong cytoplasmic and membranous positivity in the neoplastic lymphocytes. CD10 showed strong membranous positivity. BCL1 (cyclin D1) was negative. BCL6 showed strong nuclear positivity - thereby excluding marginal zone lymphoma. Ki-67 demonstrated 8–10% nuclear positivity, indicating a low proliferative index.

Figure 15: (IHC x10) Bcl 6 :Strong diffuse positivity in tumor cells

Final diagnosis: Follicular Lymphoma, Grade 1, Stage II (omental and pelvic lymph node involvement, no bone marrow infiltration).

FL is a slowly progressive NHL with a more favourable prognosis than other lymphoma subtypes.17 It originates from germinal-centre B cells and is characterised by the t(14;18) translocation, linking the BCL2 gene to the immunoglobulin heavy chain locus and resulting in BCL2 protein overexpression and inhibition of apoptosis.18 Primary mesenteric FL is rare, occurring in fewer than 1 in 200,000 cases.10,11 Despite the uncommon omental presentation, the overall prognosis remains generally positive when the disease is detected early and managed effectively, though vigilant monitoring for recurrence or histological transformation is required.10,11

4. DISCUSSION

The present case series illustrates the broad clinical and pathological spectrum of primary extranodal lymphomas across four anatomically distinct immune-privileged or unusual sites: testis, CNS, breast, and omentum. Taken together, these cases underscore several important diagnostic principles.

Pathogenesis of extranodal lymphomas. Extranodal lymphomagenesis involves a variety of mechanisms including genetic alterations, immune dysregulation, viral infection, and chronic antigenic stimulation.4 Immune-privileged sites such as the testis and CNS are characterised by down-regulated MHC class I expression and impaired immune surveillance, creating a permissive environment for lymphoid transformation.7 In these sites, DLBCL frequently harbours activating mutations in MYD88 (L265P) and CD79B — the so-called ABC-subtype signature — which may also serve as therapeutic targets for BTK inhibitor-based therapy.7

Histomorphological and IHC subtyping. Accurate lymphoma subtyping requires integration of morphology with IHC and, increasingly, molecular and cytogenetic data.12 In all four cases, B-cell lineage was confirmed by CD20 positivity and CD3 negativity. Subtyping beyond B-cell origin was refined by additional IHC: in the omental case, BCL2 and CD10 positivity, BCL1 negativity, BCL6 positivity, and a low Ki-67 collectively established the diagnosis of FL grade 1, while excluding MCL and MZL.9,17 In the breast lymphoma, negativity for epithelial (ER, PR) and neuroendocrine (synaptophysin) markers was essential to exclude carcinoma and other non-lymphoid neoplasms.7,16

Clinical implications. Because extranodal lymphomas may mimic a wide range of primary organ tumours including urological, neurological, gynaecological, and breast malignancies . Histopathology remains the gold standard for diagnosis.4,12 The omental FL case is particularly instructive: the patient's presenting complaint of menorrhagia directed clinical attention toward a gynaecological aetiology, and the lymphoma was discovered only incidentally on imaging. This reflects the well-established tendency of FL to be discovered as an incidental finding during investigations for unrelated conditions, given its indolent course.19

Management. Treatment of extranodal lymphomas follows site- and subtype-specific algorithms. For PTL, combined modality treatment with anthracycline-based chemoimmunotherapy (R-CHOP) followed by CNS prophylaxis is the standard of care, given the high risk of CNS relapse.13 PCNSL is treated with high-dose methotrexate-based regimens, often followed by consolidation.15 FL management typically involves a multidisciplinary approach encompassing surgical resection where feasible, and chemoimmunotherapy with or without rituximab for stage II or higher disease.20,21

5. CONCLUSION

This case series of four primary extranodal lymphomas ; testicular DLBCL, CNS B-cell NHL, primary breast B-cell NHL, and omental follicular lymphoma highlights the morphological diversity and diagnostic complexity encountered at rare extranodal sites. In each case, the combination of thorough histopathological examination and a targeted IHC panel was indispensable for accurate diagnosis, lymphoma subtyping, staging, and treatment planning. Clinicians and pathologists must maintain heightened awareness of extranodal lymphoma as a differential diagnosis when evaluating mass lesions at any anatomical site, including those with no inherent lymphoid tissue. Continued research, multicentre case series, and comprehensive molecular profiling will further advance our understanding of these uncommon but clinically significant entities.

Declarations

Author Contributions: All authors contributed to concept and design, data acquisition and analysis, drafting, critical review, and final approval of the manuscript.

Conflict of Interest: All authors declare no conflicts of interest.

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