Radiology Section

Primary Extranodal Lymphomas: A Case Series

TISTA BASU[1], MADHUMITA MONDAL[2], KAUSIK DAS[3], SAMIR RANA[4], UTTARA CHATTERJEE[5]

ABSTRACT

Primary Extra-Nodal Lymphomas (pENLs) comprise a heterogeneous group of disorders. pENLs are mostly Non-Hodgkin Lymphomas (NHL), although infrequent case reports of extra-nodal Hodgkin lymphomas (HL) have emerged. The most common sites for pENLs are the Gastrointestinal Tract (GIT), Central Nervous System (CNS), and head and neck region. pENLs pose a significant diagnostic challenge due to their unusual locations, a variety of confounding symptoms, and limited data available regarding their progression. Here, we present a case series of five patients of pENL: splenic HL in a 10-year-old boy, splenic NHL in a 65-year-old woman, primary ovarian lymphoma, possibly Burkitt's lymphoma, in a 22-year-old female, Primary CNS Lymphoma (PCNSL), likely Diffuse Large B-Cell Lymphoma (DLBCL), in a 67-year-old male, and a 53-year-old woman diagnosed with Primary Thyroid Lymphoma (PTL). These cases were all encountered in our tertiary care centre, and this series represents one of the first in our population. Thus, a population-specific understanding of pENLs will aid in better comprehending the disease in cases of unusual sites.

Keywords: Burkitt's lymphoma, Hodgkin, Splenic lymphoma, Thyroid lymphoma

INTRODUCTION

The pENLs are understood to be lymphomas that have predominantly extra-nodal components with little to no nodal involvement [1]. The incidence of these pENLs is increasing, which is partly due to the availability of better diagnostic modalities and a further understanding of the molecular pathogenesis of these diseases. pENLs may originate in almost any organ of the body, even in sites that are normally devoid of lymphocytes [2,3]. The most common sites of pENLs remain the GIT, CNS, and the head and neck region (such as the tonsils) [1]. About one-third of all NHL present as pENLs [4]. In light of the above understanding of pENLs, splenic lymphomas are not considered to be extra-nodal lymphomas; however, they are an extremely rare group of diseases. Primary Splenic Lymphomas (PSLs) account for less than 2% of all lymphomas and 1% of all NHLs [5].

The extra-nodal presentation of HL is far more uncommon than that of NHL. Most available literature only cites isolated case reports, making it difficult to understand the actual burden of extra-nodal HL [6-9].

CASE SERIES

Case 1

A 10-year-old boy presented with intermittent fever and abdominal swelling for one year. He soon decreased appetite and mild weight loss over the next six months. On clinical examination, he had splenomegaly but no palpable lymph nodes. The fever was mild and continuous, with no evening rise in temperature. The Erythrocyte Sedimentation Rate (ESR) was elevated (110 mm/h) when tested by the Westergren method, while other routine blood investigations were unremarkable. Malaria, dengue, and typhoid had been ruled out. Sputum for Acid-Fast Bacilli (AFB) was negative. Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), HIV, and Epstein-Barr Virus (EBV) serum tests were negative. A coronal reformatted post-contrast image of a CT scan of the whole abdomen showed an enlarged spleen (measuring 150 mm in the long axis) with a lobulated, irregularly margined, heterogeneously hypodense parenchymal mass (indicated by the yellow arrow) measuring approximately 73×69 mm, with mild patchy intralesional contrast enhancement [Table/Fig-1a].

Splenectomy was performed, and the surgical specimen was sent for histopathological examination. On gross examination, the spleen measured 15×8×6 cm, and the cut section showed multiple small whitish nodules involving most of the splenic parenchyma [Table/Fig-1b]. Haematoxylin and Eosin (H&E) stained sections revealed splenic tissue with a nodular mixed inflammatory infiltrate composed of small lymphocytes and plasma cells, along with scattered large abnormal cells having cytomorphology consistent with Reed-Sternberg (R-S) cells and mononuclear variants. There was also the presence of multiple Langhans giant cells with the formation of granulomas [Table/Fig-1c,d]. Thus, based on preliminary morphological analysis, a diagnosis of HL was considered, along with differentials such as NHL including DLBCL, ALK-positive lymphoma, and peripheral T-cell lymphoma. Infectious entities like tuberculosis and infectious mononucleosis could not be entirely ruled out.
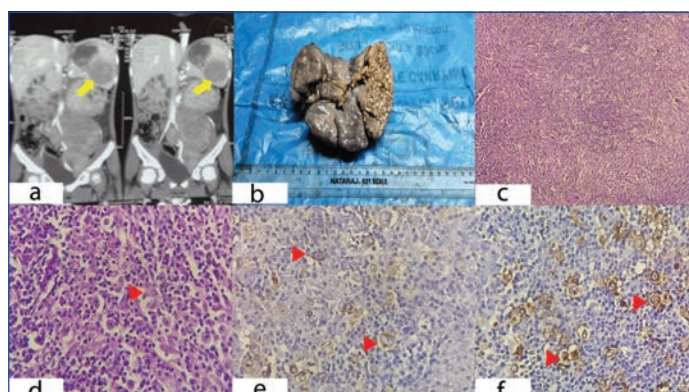
[Table/Fig-1]: a) CT scan- Coronal section showing splenic enlargement and having heterogeneously hypodense lesion with lobulated outline along with mild patchy postcontrast enhancement in the spleen (yellow arrow); b) Grossly, splenectomy specimen showing small nodules diffusely involving the splenic parenchyma in the cut-section; c) Low magnification image of the whitish nodules showing splenic architecture replaced by mixed inflammatory infiltrate composed of small lymphocytes, plasma cells, neutrophils and numerous eosinophils, with scattered admixed large abnormal cells (H&E, 100X); d) High magnification image showing the mixed inflammatory infiltrate along with occasional large atypical cells (red arrowhead) having oval to occasionally multilobate nuclei, vesicular chromatin, red nucleoli and abundant cytoplasm, consistent with Reed-Sternberg (R-S) cells and mononuclear variants (H&E, 400X); e) High magnification image showing membrane CD-15 immuno-positivity in the large, atypical cells (red arrowhead) (CD15, 400X); f) High magnification image showing membrane CD-30 immuno-positivity in the large, atypical cells (red arrowhead) (CD30, 400X).
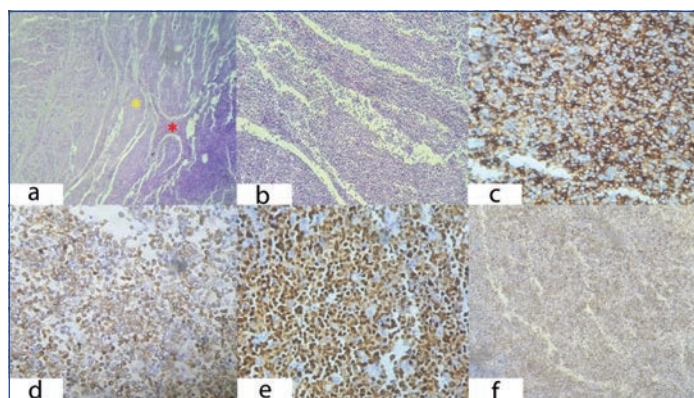
Immunohistochemical (IHC) analysis showed the large atypical cells to be strongly positive for CD-30 and CD-15, with dim immunoreactivity for PAX-5, thus confirming them as R-S cells and establishing the diagnosis of HL [Table/Fig-1e,f]. The background cells showed immunoreactivity for CD45, CD20, and CD4. The tumour cells were all immuno-negative for ALK, EMA, vimentin, BCL-6, and BCL-2, thus ruling out the possibility of NHLs. Ziehl-Neelsen (Z-N) stained smears were non-contributory. A bone marrow biopsy performed for staging of the disease revealed a reactive marrow picture. The patient received chemotherapy with the doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) regimen and reported no recurrence of lymphoma in any other sites during the one-year follow-up.

Case 2

A 65-year-old female patient presented with dyspnoea, chest discomfort, and abdominal pain for eight months. Clinical examination revealed non-tender grade 3 splenomegaly, according to the Hackett grading system for palpable splenomegaly [10]. Routine haematological and biochemical examinations showed anaemia and thrombocytopaenia, with consistently elevated CRP levels. Bone marrow aspiration revealed a reactive marrow picture. A CECT of the whole abdomen reported multiple heterogeneous masses and hypodensities within a necrotic core in the spleen, indicating a neoplastic aetiology, along with enlarged mesenteric lymph nodes.

Splenectomy was performed, and the specimen was sent for histopathological examination. Grossly, the spleen measured 22×14×07 cm, and the cut section revealed a whitish variegated growth with areas of haemorrhage. The attached omentum showed the presence of enlarged lymph nodes and nodules. Microscopy of the representative sections demonstrated a micro-nodular tumoural infiltrate centred around the white pulp areas. The interior of these follicles consisted of smaller, darkly staining lymphocytes, while the marginal zone cells were larger and more pale. The red pulp was also infiltrated by this latter group of cells, arranged in both cords and sinuses. The overall histomorphological features were consistent with splenic NHL, possibly Splenic Marginal Zone Lymphoma (SMZL) [Table/Fig-2a,b].

The differential diagnoses considered included Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL), mantle cell lymphoma, Hairy Cell Leukaemia (HCL), follicular lymphoma, and Lymphoplasmacytic Lymphoma (LPL). The IHC findings were as follows: BCL2, PAX5, CD45, and CD20 were positive, whereas BCL6, CD10, cyclin D1, CD5, CD79a, and Annexin A1 were negative [Table/Fig-2c-e]. The Ki-67 labeling index was up to 60% [Table/Fig-2f].

The immuno-negativity for CD5 ruled out CLL/SLL, while the absence of cyclin D1 expression rules out mantle cell lymphoma. The immuno-negativity for Annexin A1 rules out HCL. The lack of CD10 and BCL6 expression helped to exclude follicular lymphoma. LPL showed monocytoid B cells in the marginal zone and lacked a pale corona surrounding the reactive germinal centres, which is unlike the histomorphological findings in this case.

The patient was treated with Rituximab chemotherapy along with splenectomy due to the high proliferative index. The patient is doing well at the 18-month follow-up.

Case 3

A 22-year-old primipara female presented with lower abdominal pain and distention for two months. Except for anaemia, her routine haematological findings were within normal limits. Serum LDH and CA-125 levels were elevated. A CECT scan of the whole abdomen was performed and showed (in the axial section at the level of the lower abdomen) evidence of a bulky, lobulated, almost symmetrical, and homogeneously enhancing mass involving both ovaries (L-Left ovary, R- Right ovary) [Table/Fig-3a]. No lymphadenopathy was present. Bone marrow examination was unremarkable. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The gross examination revealed that the right ovarian mass measured 19×9×4 cm, while the left ovarian mass measured 18×11×7 cm. The cut sections of both ovaries were white and fleshy [Table/Fig-3b]. Microscopically, representative sections from both ovaries showed neoplastic cells arranged in a diffuse pattern. The tumour cells were medium-sized, round to oval in shape, with coarse chromatin and basophilic nucleoli. Mitoses and apoptotic bodies were abundant [Table/Fig-3c]. No R-S cells were found. IHC studies showed the tumour cells to be positive for CD-45, PAX-5, BCL-6, CD-10, and CD-20 [Table/Fig-3d,e], while they were immuno-negative for CD-5, Cyclin-D1, CD-15, CD-30, and BCL-2. The Ki-67 proliferation index was 98% [Table/Fig-3f]. Thus, the overall histopathological and IHC features indicated a primary NHL of B-cell origin, possibly Burkitt's lymphoma. Primary ovarian lymphomas are usually managed with chemotherapy and surgical resection, both of which were employed in this case. The patient regained regular menstrual cycles and reported no relapse symptoms even after one year of follow-up.
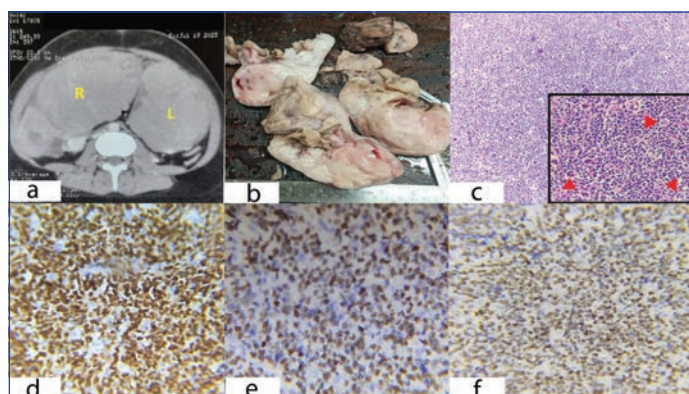

[Table/Fig-2]: a) Scanner magnification image showing micro-nodular tumoural infiltrates centred around the white pulp areas. The darkly staining lymphocytes (red asterisk) form the interior of these follicles while the ones in the marginal zone are slightly more pale (yellow asterisk). (H&E, 40X); b) Low magnification image showing the darkly staining lymphocytes forming the interior of these follicles while the ones in the marginal zone are slightly more pale. (H&E, 100X); c) High magnification image showing diffuse cytoplasmic membrane positivity for CD-45 in the tumour cells. (CD45; 400X); d) High magnification image showing diffuse cytoplasmic membrane positivity for CD-20 in the tumour cells. (CD20; 400X); e) High magnification image showing nuclear positivity for PAX-5 in the tumour cells. (PAX-5; 400X); f) Low magnification image of the Ki-67 labelling index of 60% (Ki-67; 100X).

[Table/Fig-3]: a) CT scan- Axial section showing evidence of neoplastic lesions involving bilateral ovaries (R and L) along with mild ascites; b) Gross images of bilateral ovaries appearing fleshy and whitish; c) Low magnification image of the tumour showing neoplastic cells arranged in a diffuse pattern and the high magnification image (inset) showing the medium sized round to oval tumour cells with coarse chromatin and basophilic nucleoli (red arrowheads) {H&E, 100X and 400x (inset)}; d) High magnification image showing nuclear positivity for PAX-5 in the tumour cells (PAX-5; 400X); e) High magnification image showing nuclear positivity for BCL-6 in the tumour cells (BCL-6; 400X); f) High magnification image of the Ki-67 labelling index of 98% (Ki-67; 400X).

Case 4:

A 67-year-old male presented with headaches, lethargy, and drowsiness for the past four months. Imaging (CECT brain; axial section at the level of the third ventricle) revealed a relatively defined, lobulated, mild, and homogeneous hyperdense lesion (indicated by

a yellow asterisk) measuring 36 x 44 mm (in anteroposterior and transverse dimensions, respectively) in the periventricular region, crossing the midline. The lesion showed moderate, homogeneous post-contrast enhancement {pre-contrast (left-side image) attenuation +45 HU and post-contrast (right-side image) attenuation +68 HU} [Table/Fig-4a]. These features were suggestive of primary lymphoma. No significant lymphadenopathy was identified clinically.

On histopathological examination, medium-sized round cells were observed infiltrating the brain parenchyma, demonstrating a significant angiocentric pattern. These cells exhibited vesicular chromatin and occasionally showed prominent nucleoli [Table/Fig-4b,c]. Immunohistochemistry revealed that the tumour cells were immunopositive for CD45, CD20, and PAX-5, while CD10 and BCL-6 were immunonegative [Table/Fig-4d]. The Ki-67 labeling index was 55% [Table/Fig-4e].
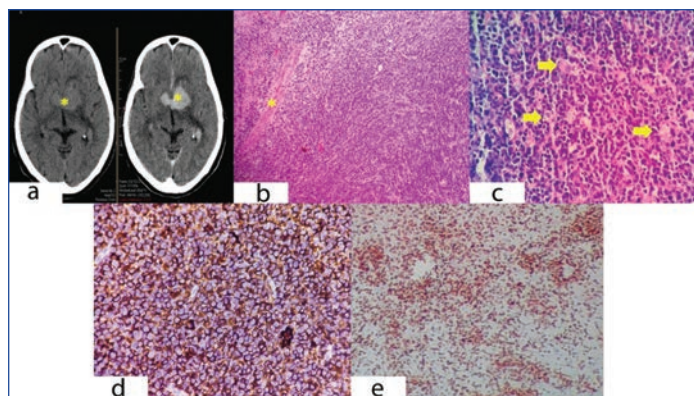
[Table/Fig-4]: a) CECT brain- axial section showing homogeneously hyperdense lesions (yellow asterisk) in the periventricular region, crossing the midline and showing homogeneous post-contrast enhancement; b) Low magnification image of the tumour showing medium sized lymphoid cells infiltrating the brain parenchyma and showing a significant angio-centric pattern (yellow asterisk) (H&E; 100X); c) High magnification image showing the lymphoid cells having vesicular chromatin and occasionally showing prominent nucleoli (yellow arrow) (H&E; 400X); d) High magnification image showing diffuse cytoplasmic membrane positivity for CD-20 in the tumour cells (CD20; 400X); e) Low magnification image of the Ki-67 labelling index of 55% (Ki-67; 100X).

Based on these findings, a diagnosis of NHL of B-cell origin, possibly DLBCL, was made. The patient received steroids, methotrexate-based chemotherapy, and irradiation; however, he succumbed to his disease within six months.

Case 5

A 53-year-old female presented with a thyroid swelling that had been present for the last 10 years but had begun to grow rapidly in size over the past six months. She complained of dyspnoea. On physical examination, both thyroid lobes were enlarged, firm in consistency, and non-tender, accompanied by enlargement of the level VI cervical lymph nodes. Thyroid function tests indicated hypothyroidism. A Fine-Needle Aspiration Cytology (FNAC) was conducted, and the report suggested lymphocytic thyroiditis (Bethesda category II). A total thyroidectomy was performed to relieve the patient's immediate symptoms, and the specimen was sent for histopathological examination.

Gross examination revealed that the cut sections of both lobes and the isthmus showed multiple small whitish areas along with haemorrhagic areas. Microscopically, sections from both lobes and the isthmus exhibited sheets of monomorphic lymphoid cells infiltrating the thyroid parenchyma and almost entirely replacing its native follicular architecture [Table/Fig-5a,b].

On immunohistochemistry, the lymphoid cells were positive for CD-19 and CD-5 [Table/Fig-5c,d], while being negative for CD-10, BCL-6, cyclin D1, and SOX-11 [Table/Fig-5e]. The Ki-67 labeling index was 5% [Table/Fig-5f]. In light of the overall features, a diagnosis of NHL of B-cell origin was suggested. The total thyroidectomy proved to be curative for the patient, and she was not subjected to any further

treatment modalities. The patient was doing well at the 18-month follow-up.
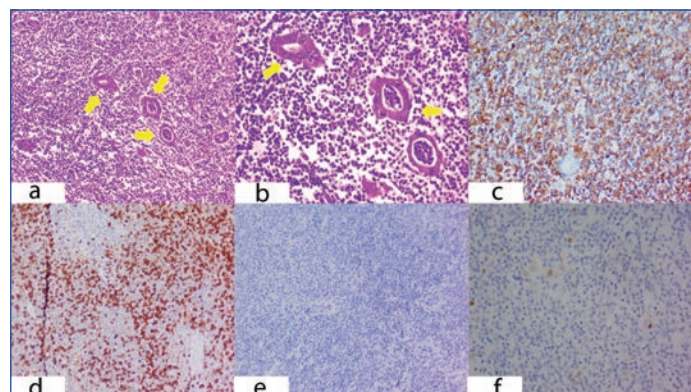
[Table/Fig-5]: a) Low magnification image showing sheets of monomorphic lymphoid cells infiltrating the thyroid parenchyma and almost entirely replacing the native follicular architecture (yellow arrows marking the remnant thyroid follicles) (H&E; 200X); b) High magnification image showing the lymphoid cells having hyperchromatic nuclei and scanty cytoplasm and few remnant thyroid follicles (yellow arrows) (H&E; 400X); c) Low magnification image showing diffuse cytoplasmic membrane positivity for CD-19 in the tumour cells. (CD19; 200X); d) Low magnification image showing diffuse cytoplasmic membrane positivity for CD-5 in the tumour cells. (CD5; 200X); e) Low magnification image showing immune-negativity for SOX-11 in the tumour cells. (SOX-11; 100X); f) High magnification image of the Ki-67 labelling index of 05% (Ki-67; 400X).

DISCUSSION

Extra-nodal lymphomas can arise in almost any organ, but the most common locations are the GIT and the head and neck region, particularly the tonsils and Waldeyer's ring [11]. The distribution of histologic subtypes is known to be site-specific. Immune-privileged sites, such as the CNS and testis, often show large B cell lymphomas, while the GIT exhibits a wider spectrum of lymphoma types, including DLBCL, MALToma, mantle cell lymphoma, and follicular lymphoma [11]. The histologic subtype is a more important prognostic determinant than the site of disease, even for pENLs.

PSL do not essentially classify as pENLs; nonetheless, they are a rare entity [5]. They pose a considerable diagnostic challenge due to vague presenting symptoms such as abdominal discomfort, fever, and abdominal tenderness. A histopathological diagnosis is thus of utmost importance to ensure appropriate management. FNAC or core biopsies are usually not preferred due to the risk of possible haemorrhage, especially in a massively enlarged spleen. PSL may present with cytopenias and/or elevated ESR [5]. Elevated serum LDH levels are a non-specific but consistent finding in PSLs [12]. Splenectomy is important from both a diagnostic and therapeutic perspective [13]. Adverse prognostic factors for PSLs include advanced stage, high prognostic index, and immuno-positivity for BCL-2, BCL-6, and MYC [12,14,15].

Grossly, the splenic involvement of different PSLs varies to a certain extent, providing diagnostic clues to differentiate one from another. Primary Splenic DLBCL (PS-DLBCL) typically involve the white pulp and present as single or multiple hypodense lesions. In the more indolent PSLs or secondary splenic lesions, tumours may infiltrate the entirety of the spleen or predominantly affect the red pulp. SMZL usually presents with marked splenomegaly and lymphadenopathy. The splenic involvement of HL typically appears as diffuse splenic infiltration [16].

Splenectomy, along with adjuvant chemotherapy, has been shown to improve the five-year survival rate for PSLs [17].

pENLs involving the female genital tract are extremely rare overall, but the ovary is the most common site of pENL in relation to the female tract. An incidence of 0.1-0.5% has been reported for primary ovarian NHLs [18]. Both B- and T-cell lymphomas may be encountered, but the former is more common. DLBCL is the most frequently encountered histological type of NHL in the ovary [19]. Burkitt lymphoma has been reported in the literature but is usually seen in children or young adults [20].

There is much speculation regarding the pathogenesis of primary ovarian lymphomas. One theory suggests that they arise from reactive lymphocytic infiltration in response to pelvic inflammatory disease, endometriosis, and other similar inflammatory conditions [21]. Patients may present with complaints indistinguishable from those of any other primary ovarian malignancy, such as abdominal discomfort, abdominal distension, and menstrual irregularities; often, B symptoms are also reported [19]. Radiology and serum markers like CA-125 often fail to provide any specific diagnostic clues for primary ovarian lymphoma. Histopathological examination, along with IHC analysis, remains the mainstay of diagnosis.

Morphological differentials to be considered include dysgerminoma, granulosa cell tumour, small cell neuroendocrine carcinoma, small cell carcinoma of the hypercalcemic type, and undifferentiated carcinomas [22]. Adverse outcomes have been related to the complications of radical surgery rather than to the actual disease. High levels of CA-125 have shown some correlation with a lower response to treatment and a more aggressive disease [23]. Similar to Primary Systemic Lymphomas (PSLs), serum LDH levels are also elevated in ovarian lymphomas. Recovery of the menstrual cycle and spontaneous pregnancy in women undergoing chemotherapy for ovarian lymphomas have been reported previously [24].

PCNSLs are characterised by the exclusive and primary involvement of the brain, spinal cord, leptomeninges, and eyes. They are a rare subtype of NHL, accounting for up to 3% of all NHLs and about 3% of primary brain tumours [25]. Acquired or congenital immunosuppression is a well-established risk factor for developing PCNSLs. PCNSL is an AIDS-defining illness, and 100% of cases are associated with an EBV infection, although this may not be the case for PCNSLs in immunocompetent individuals [26]. The median age at presentation for the latter group is in the 7th decade of life [27]. The majority of PCNSLs are DLBCLs, while a minority consists of T-cell lymphomas, Burkitt lymphomas, lymphoblastic lymphomas, and marginal zone lymphomas [28]. The latest (5th) edition of the WHO classification has created a new umbrella category for large B-cell lymphomas occurring in immune-privileged sites, which are walled off by their respective barriers, namely the CNS, testis, and the vitreo-retinal compartment [29]. These lymphomas share immunophenotypic and molecular features.

Patients may present with non-specific focal neurological deficits, symptoms of raised intracranial pressure, neuropsychiatric symptoms, and seizures, depending on the location of the lesion. Ocular involvement is a common occurrence in cases of PCNSLs. Routine work-ups for PCNSLs includes contrast-enhanced MRIs, stereotactic biopsies, lumbar punctures for Cerebrospinal Fluid (CSF) examination, and ophthalmologic evaluations. Histopathological examination is characterised by an angiocentric growth pattern, along with diffuse infiltration of the brain parenchyma by small clusters or individual neoplastic cells against a background of mixed inflammation [27]. Differential diagnoses to consider for PCNSLs include high-grade gliomas, metastatic lesions, demyelinating pseudotumours, and granulomatous lesions [30].

Prognosis can be determined by one of two prognostic models: the Memorial Sloan Kettering Cancer Centre model (which includes only age and performance status) and the International Extranodal Lymphoma Study Group (IELSG) model (which includes age and performance status, along with serum lactate dehydrogenase level, CSF protein concentration, and involvement of deep structures of the brain) [31,32]. Patients with no or only one risk factor have a fairly favourable overall survival rate, which decreases with an increasing number of applicable risk factors [32]. PCNSLs are both chemo- and radiosensitive, but the overall response rates and long-term survival are inferior to those seen in similar subtypes of extranodal NHL [33].

PTLs are uncommon, accounting for less than 2% of ENLs and up to 5% of thyroid neoplasms [3]. They are seen more often in elderly women. Patients with PTLs typically present with vague, non-specific symptoms similar to those of other thyroid lesions, such as an enlarging neck mass, which may be associated with complaints of dysphagia, dyspnoea, and features of hypothyroidism.

Diagnostic modalities, such as Ultrasound (USG), Contrast-Enhanced Computed Tomography (CECT) of the neck, and thyroid function tests, may provide diagnostic clues. FNAC may also be performed. Cytological smears usually reveal an increased population of lymphocytes [34]. The cytological differential diagnosis includes lymphocytic thyroiditis, in which the lymphocytes are small, mature lymphocytes, as opposed to the large blast-like lymphocytes seen in a PTL. Additionally, PTLs typically show infrequent or absent thyroid follicular cells with oncocytic change. PTLs often arise against a background of autoimmune thyroiditis, such as Hashimoto's thyroiditis, which may pose a challenge for accurate cytological diagnosis [35].

PTLs are most commonly DLBCLs or Mucosa-Associated Lymphoid Tissue (MALT) lymphomas. The disease may disseminate, often to the GI tract rather than the CNS. Surgery is not considered a curative treatment modality but may be performed in emergency cases where dyspnoea and dysphagia pose an immediate threat to life. Chemotherapy and radiotherapy regimens are well-established for both DLBCL and MALT lymphomas.

Most studies identify tumour size (greater than 10 cm) as the most important prognostic factor [36-38]. Other poor prognostic factors include older age (over 60 years), presence of extra-thyroid extension, high-grade NHL, advanced stage, short duration of symptoms (less than 6 months), tumour fixation, and mediastinal involvement [39].

CONCLUSION(S)

pENLs are a heterogeneous group of diseases and pose a considerable diagnostic challenge due to their varied sites and non-specific presentations. Accurate histological categorisation is important from both therapeutic and prognostic perspectives. An accurate diagnosis of a pENL requires thorough clinical, radiological, biochemical, and occasionally haematological correlation, along with histopathological and IHC examinations.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pathology, IPGMER, Kolkata, West Bengal, India.
2. Assistant Professor, Department of Pathology, IPGMER, Kolkata, West Bengal, India.
3. Junior Resident, Department of Pathology, IPGMER, Kolkata, West Bengal, India.
4. Associate Professor, Department of Radiodiagnosis, Dr. B.C. Roy Multi Speciality Medical Research Centre, I.I.T, Kharagpur, West Bengal, India.
5. Professor, Department of Pathology, IPGMER, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Samir Rana,
NFA-118, IIT KGP Campus, Kharagpur-721302, West Bengal, India.
E-mail: dr.samirrana@gmail.com