Case Report

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Pathology Section

A Case of Primary CNS Diffuse Large B-cell Lymphoma Mimicking Glioblastoma: A Diagnostic Conundrum

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ABSTRACT

Primary Central Nervous System-Diffuse Large B-cell Lymphoma (PCNS-DLBCL) is a rare extranodal lymphoma that can mimic high-grade gliomas on imaging and histology, causing diagnostic delays. We report a 72-year-old immunocompetent man with hypertension and diabetes who presented with sudden-onset aphasia. MRI revealed a left frontal intra-axial lesion and additional supratentorial enhancing foci, suggestive of glioblastoma or metastases Stereotactic biopsy showed sheets of large atypical cells with perivascular clustering, necrosis, and mitoses. Glioma markers (GFAP, IDH1 R132H, p53) were negative in tumour cells, while GFAP highlighted reactive glia. Immunohistochemistry revealed strong membranous CD20 positivity, BCL2 and c-MYC expression (~50–60% of tumour cells), CD10 negativity, and a high Ki-67 index (70–80%), consistent with high-grade PCNS-DLBCL. Epstein–Barr virus-encoded RNA (EBER) in situ hybridisation was negative. The patient received high-dose Methotrexate (MTX) and was tumour-free at 12 months follow-up.This case underscores that imaging and morphology alone may be misleading, and comprehensive immunophenotyping is critical for accurate diagnosis and appropriate therapy.

Keywords: Brain tumour, Central nervous system, Diffuse large B-cell lymphoma, Glioma mimic, Immunohistochemistry, Primary CNS lymphoma

CASE REPORT

A 72-year-old male patient with type 2 diabetes mellitus and hypertension presented with sudden-onset aphasia. His medications included Tablet Glycomet, taken three times daily for 10 years; Tablet Udapa 10 mg and Tablet Telsar 40 mg for 15 years; Capsule Ecosprin for 7 years; and Capsule Absolut as a nutritional supplement for 7 years.

MRI revealed a large intra-axial Space-Occupying Lesion (SOL) in the left frontal lobe with multiple heterogeneously enhancing supratentorial lesions, suggestive of high-grade glioma or metastases. Laboratory tests, including routine haematology and biochemistry, were within normal limits. HIV serology was negative, and serum Lactate Dehyrogenase (LDH) was slightly elevated.

Stereotactic biopsy yielded multiple soft tissue bits measuring 1.8×1×0.5 cm in aggregate [Table/Fig-1]. Microscopically, the tumour comprised sheets of atypical cells with round to oval nuclei, coarse chromatin, and moderate cytoplasm [Table/Fig-2]. Foci of microvascular proliferation, necrosis, and brisk mitoses (12–15/10 HPF) were observed [Table/Fig-3]. Background brain showed reactive gliosis and entrapped neurons. Lymphoglandular bodies were also noted.

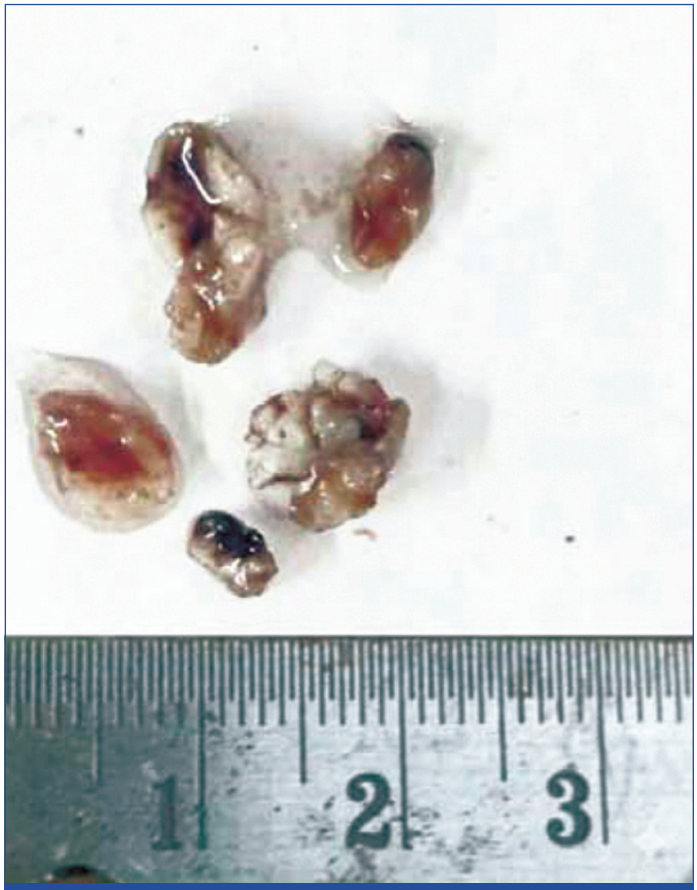
Glioma-specific Immunohistochemistry (IHC) showed tumour cells negative for GFAP, IDH1 R132H, and p53 [Table/Fig-4a-b], while GFAP highlighted reactive glia [Table/Fig-4a].

Given the lack of glial differentiation, a lymphoma panel was performed. Tumour cells showed strong membranous CD20 positivity [Table/Fig-5a], BCL2 expression [Table/Fig-5b], c-MYC expression (50–60% of tumour cells) [Table/Fig-6a], and CD10 negativity, with scattered CD3-positive T-cells in the background, confirming a high-grade, non–germinal center PCNS-DLBCL.The Ki-67 proliferation index was 70–80% [Table/Fig-6b]. Epstein–Barr virus-encoded RNA (EBER) in situ hybridisation was negative.

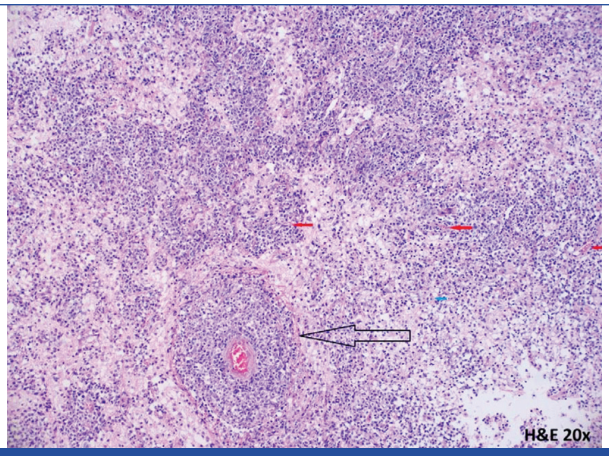
The patient received high-dose methotrexate and was tumour-free at 12 months follow-up.

DISCUSSION

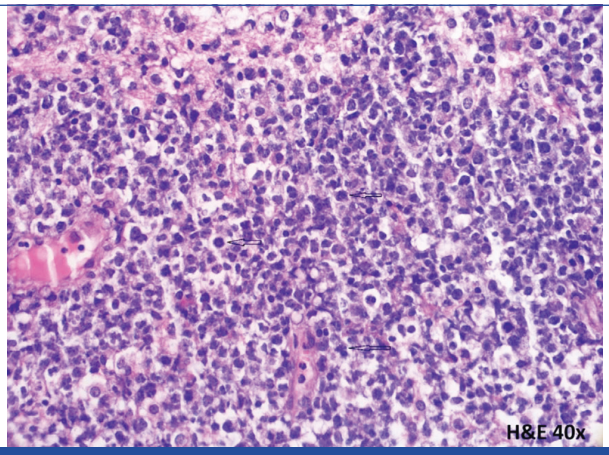
Primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL) is an uncommon, aggressive extranodal lymphoma confined to the brain, leptomeninges, spinal cord, or eyes.The 2021 WHO Classification of Central Nervous System (CNS) Tumours recognises PCNSL as a distinct lymphoid neoplasm under the category of “Mature



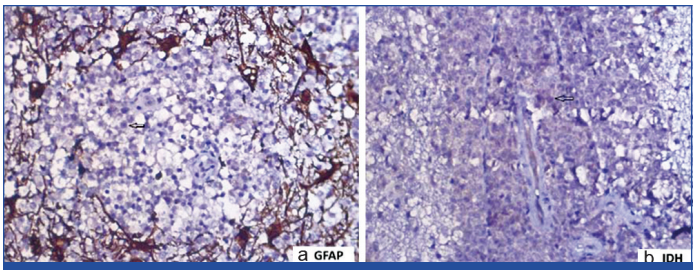
[Table/Fig-1]: Gross appearance of biopsy tissue showing multiple grey-white soft tissue bits.



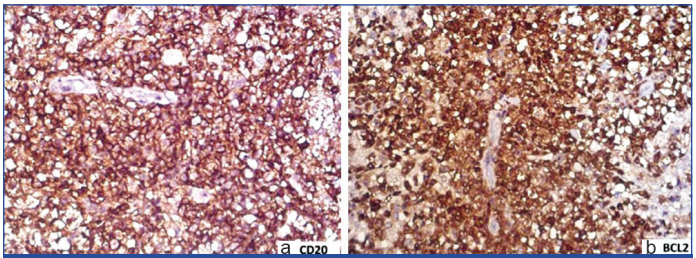
[Table/Fig-2]: Low-power view (H&E, 100x) showing sheets of atypical large lymphoid cells with perivascular clustering(black arrow) in brain parenchyma, microvascular proliferation (red arrow), lymphoglandular bodies (blue arrow).



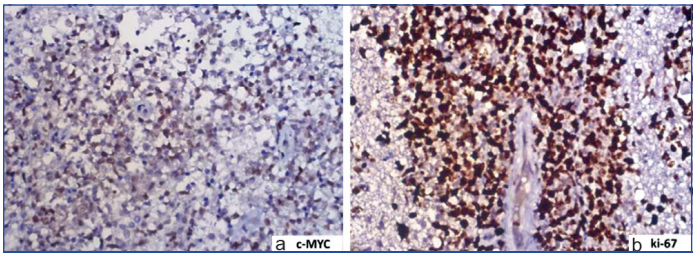
[Table/Fig-3]: High-power view (H&E, 400x) demonstrating large atypical cells with coarse chromatin, mitoses (arrow), necrosis, and microvascular proliferation.



[Table/Fig-4]: a) GFAP highlighting reactive glial cells; tumour cells are negative (400x); b) IDH1 R132H negative in tumour cells, internal control positive.



[Table/Fig-5]: Immunohistochemistry: a) CD20 strong membranous positivity; b) BCL2 expression in tumour cells (400x).



[Table/Fig-6]: Immunohistochemistry: a) c-MYC expression (50–60% of tumour cells); b) Ki-67 proliferation index (70–80%) (400x).

B-cell neoplasms", predominantly of activated B-cell phenotype, and emphasises the importance of integrating histopathological, immunophenotypic, and molecular features for diagnosis [1]. This refined classification underscores the critical need for accurate identification, as clinical, radiological, and morphologic features often overlap with other high-grade CNS malignancies such as glioblastoma.

Histopathologically, PCNS-DLBCL is characterized by diffuse sheets of large atypical lymphoid cells, angiocentric infiltration, and brisk mitotic activity. However, reactive changes, necrosis, and microvascular proliferation may obscure the classic morphology, causing confusion with high-grade gliomas.Lauw et al. provided a detailed diagnostic overview emphasizing that microvascular proliferation and necrosis—classically attributed to glioblastoma—can occasionally be seen in PCNSL, complicating histological distinction [2]. In the present case, perivascular clustering was evident, yet the accompanying necrosis and vascular proliferation led to an initial misdiagnosis of glioblastoma. The diagnosis was ultimately confirmed on immunohistochemistry, which revealed diffuse CD20 positivity and absence of glial fibrillary acidic protein (GFAP), consistent with PCNS-DLBCL.

Comparison with published Indian data highlights similarities and differences. Rao S et al., reported a large Indian cohort of 143 cases of primary CNS diffuse large B- cell lymphoma, noting frequent deep brain involvement and multifocal presentation. Such radiological patterns, particularly when accompanied by necrosis, may overlap with high-grade gliomas. Our case exemplifies this diagnostic challenge and highlights the indispensable role of immunohistochemistry in establishing the correct diagnosis [3]. Our case mirrors this diagnostic challenge, demonstrating that even in immunocompetent elderly patients, imaging and morphology can be misleading. Other reports, such as Luo S et al., describe rare CD20-negative variants, reinforcing that immunophenotypic evaluation is indispensable [4].

Radiologically, PCNSL classically presents as homogeneously enhancing deep-seated lesions with restricted diffusion, but atypical appearances—heterogeneous enhancement, cortical or subcortical localization, or central necrosis—may mimic glioblastoma [5,6]. Traditional MRI parameters alone are often insufficient for confident differentiation. Recent imaging studies demonstrate that advanced modalities can improve diagnostic accuracy. Multiparametric MRI and diffusion tensor imaging can identify microstructural differences between glioblastoma and PCNSL, as PCNSL tends to show lower relative cerebral blood volume and higher diffusion restriction [7]. Quantitative diffusion imaging further refines these distinctions, showing reproducible microstructural signatures unique to PCNSL [8]. Additionally, novel molecular imaging techniques such as 68Ga-Pentixafor PET combined with MRI have shown high sensitivity and specificity in differentiating the two tumours, offering a promising noninvasive adjunct to tissue diagnosis [9].

Despite these advances, histopathological confirmation remains indispensable. PCNSL often shows deceptively glial-like morphology on small biopsies due to high cellularity and reactive gliosis. As emphasised by Lauw MIS et al., a comprehensive immunohistochemical panel is essential to confirm the diagnosis and avoid misclassification [2]. Emerging diagnostic tools, including cerebrospinal fluid biomarkers—such as Interleukin-10 (IL-10), CXCL13, MYD88 L265P mutation, and immunoglobulin clonality assays—are being explored to facilitate earlier and less invasive diagnosis [10]. However, these remain investigational and are not yet part of routine practice in many centers.

From a therapeutic standpoint, distinguishing PCNSL from glioblastoma is clinically imperative because management strategies differ substantially. PCNSL is treated primarily with high-dose methotrexate-based chemotherapy, often combined with rituximab and consolidation radiotherapy, whereas glioblastoma management relies on maximal surgical resection followed by

concurrent chemoradiation with temozolomide [11]. Surgical resection is generally avoided in PCNSL due to its diffuse and infiltrative growth pattern, which limits the benefit of debulking [2,11]. Nayak L and Batchelor TT emphasised that early and accurate diagnosis directly influences survival, as inappropriate glioblastoma-directed therapy may lead to disease progression and poorer outcomes [11]. Recent reviews reaffirm that high-dose methotrexate remains the backbone of therapy, with newer regimens incorporating targeted or immunomodulatory agents showing improved response rates [12].

Prognostically, PCNSL carries a poorer outcome compared with systemic DLBCL, particularly in older patients. However, when diagnosed early and treated appropriately, remission and prolonged survival are achievable [11,12]. Our patient, an elderly immunocompetent individual, responded favourably to methotrexate-based therapy, aligning with outcomes reported in contemporary literature.

In summary, this case highlights the diagnostic complexity of PCNS-DLBCL mimicking glioblastoma, particularly in immunocompetent elderly patients. Reliance on imaging and morphology alone is insufficient; a combination of immunohistochemistry and, where available, molecular diagnostics ensures accuracy. The incorporation of recent WHO classification principles and awareness of modern imaging adjuncts can minimize misdiagnosis and guide optimal patient management.

CONCLUSION(S)

Primary central nervous system diffuse large B-cell lymphoma has a worse prognosis than systemic diffuse large B-cell lymphoma. Imaging and morphology alone do not allow reliable discrimination from other malignant brain tumours or space-occupying inflammatory lesions. It is crucial to differentiate PCNS-DLBCL from other brain malignancies such as glioblastoma, as the treatment modalities for both vary significantly. Therefore, a high index of suspicion warrants consideration of immunohistochemistry for confirmation.

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