



Autopsy and Case Reports

ISSN: 2236-1960

Hospital Universitário da Universidade de São Paulo

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Autopsy and Case Reports, vol. 11, e2021250, 2021
Hospital Universitário da Universidade de São Paulo

DOI: <https://doi.org/10.4322/acr.2021.250>

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Primary diffuse large B-cell lymphoma of the CNS, with a "Lymphomatosis cerebri" pattern

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How to cite: Thirunavukkarasu B, Gupta K, Shree R, Prabhakar A, Kapila AT, Lal V, Radotra B. Primary diffuse large B-cell lymphoma of the CNS, with a "Lymphomatosis cerebri" pattern. *Autops Case Rep* [Internet]. 2021;11:e2021250. <https://doi.org/10.4322/acr.2021.250>

ABSTRACT

We describe an unusual case of lymphomatosis cerebri in a middle-aged lady presenting with rapid-onset dementia. The lymphomatous infiltrate, instead of forming mass lesions, percolated throughout the brain parenchyma, which is often missed on a stereotactic biopsy and hence warrants caution and awareness about this entity. The nonspecific symptoms at presentation and a variable picture at imaging make this entity diagnostically challenging.

Keywords

Central Nervous System Neoplasm; Lymphomatosis cerebri, Non-Hodgkin lymphoma; Dementia

Highlights:

- Primary CNS Lymphoma rarely has a distinct pattern described as lymphomatosis cerebri
- Clinically may present with rapid onset dementia
- Identifying this lesion on imaging is challenging, as features are variable, presence of extensive signal abnormalities on MRI in the lobar white matter and deep nuclei without corresponding mass effect or enhancement is highly suggestive of this lesion
- Warrants caution while reporting stereotactic biopsy as cells spread along the parenchyma instead of forming mass lesions

for 2% of primary tumors of CNS.¹ It is confined to the brain, spinal cord, and eyes without systemic involvement. The majority of PCNSL are composed of diffuse large B-cell lymphoma (DLBCL) (90-95%) followed by Burkitt lymphoma (<5%), lymphoblastic lymphoma (<5%), marginal zone lymphoma (<3%), and T-cell lymphoma (2-3%).^{2,3} PCNSL usually presents as a well-demarcated, unifocal, or multifocal lesion in the brain. A rare morphological variant of PCNSL is lymphomatosis cerebri (LC). Drawing an analogy from gliomatosis cerebri, Bakshi et al.⁴ coined the term 'lymphomatosis cerebri' for this unique pattern of PCNSL wherein the atypical lymphoid cells strut across the entire brain parenchyma without causing any cohesive mass. LC has been described in anecdotal case reports.^{5,6} Its clinical presentation as rapidly progressive

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma accounting

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dementia with heterogenous imaging features makes this entity diagnostically challenging. Moreover, the subtle passive infiltration of the brain parenchyma by atypical lymphoid cells mandates caution when evaluating small biopsies.

CASE REPORT

A 48-year-old immunocompetent female patient presented with a subacute (two months history of new-onset seizures) history of generalized seizures followed by right hemiparesis, headache, and vomiting. Her weakness improved completely after she received steroids at an outside center; however, her condition deteriorated rapidly over the next 2 weeks to altered sensorium, and she was referred to our institute for further evaluation. At the presentation, she was stuporous. There was spontaneous eye-opening; however, she was not responding to commands. There was a paucity of movements and hyperreflexia in the right upper and lower limbs, plantar withdrawal response on the right side, and extensor on the left side. The Glasgow coma scale was 10, and the modified Rankin scale was 5. The gadolinium-enhanced magnetic resonance imaging (MRI) of the brain suggested multifocal areas of altered signal intensities involving cortical as well as deep gray matter, subcortical and deep white matter, as well as the corpus callosum, with patchy areas of enhancement, minimal mass effect, and focal areas of diffusion restriction. There was no evidence of hemorrhage (Figures 1A to 1D). The HIV serology was negative.

The cerebrospinal fluid (CSF) analysis (Table 1) revealed lymphocytic pleocytosis along with normal protein and glucose levels.

Table 1. Cerebral spinal fluid examination

| | | |
|----------------------|-------------------------|-------|
| Protein (mg/dl) | 33 | 15-60 |
| Glucose (mg/dl) | 51 | 45-80 |
| Cytology | Lymphocytic pleocytosis | - |
| Gram stain | Negative | - |
| Culture | Sterile | - |
| India ink | Negative | - |
| Cryptococcal antigen | Negative | - |
| Ziehl-Neelsen stain | Negative | - |
| HSV PCR | Negative | - |

HSV PCR: Herpes simplex virus polymerase chain reaction

The laboratory workup is shown in Table 2.

The Chest X-ray was normal, as well as the abdominal ultrasonography. The contrast-enhance computed tomography showed a well-defined homogeneous thin-walled cyst (2.5x 2.7x 3.4 cm) in the left ovary, likely a functional cyst. The PET-CT discarded any extracerebral or systemic lymphoma. On repeating imaging, a week later, there was a gross increase in the lesions with supratentorial herniation. She deteriorated rapidly and succumbed to her illness after five days of hospital stay. Due to rapidly progressive disease, possibilities of malignancy (lymphoma versus diffuse glioma), fulminant demyelination, fungal or parasitic infection were kept, and a brain autopsy was performed.

The brain, at autopsy, weighed 1300 g (mean Reference range 1240 g). There were no exudates on the convexities of the brain base. The leptomeninges were translucent. There were mild uncus notching and tonsillar herniation, indicating cerebral edema. Coronal slices revealed focal prominence of the intraparenchymal vessels in all the slices. No focal lesions were identified. The striate cortex showed softening and irregular grey-white junction bilaterally (Figures 2A to 2C).

The brain stem, cerebellum, and upper part of the cervical cord appeared normal on gross examination. Microscopic sections from the striate cortex revealed the maximum burden of the disease with a subarachnoid collection of atypical lymphocytes, characterized by round to oval in shape and twice the size of mature lymphocytes. Nucleolar prominence was noted occasionally. These were seen percolating along the entire grey matter and white matter without forming mass lesions (Figures 3A and 3B). There was a modest tendency to aggregate around the vessels. The remaining frontal cortex, cingulate gyrus, amygdala, hippocampus, central white matter, basal ganglia showed a very scant and delicate infiltrate of similar cells strutting through the parenchyma characteristic of LC pattern noted in primary CNS Diffuse large B cell lymphoma. (Figure 3C). Neoplastic cells were positive for CD20 (Figure 3D), MUM1, Ki 67 of 70%, while negative for CD10, Bcl6, CD138. CD3 and CD68 highlighted very few T lymphocytes and macrophages. EBER-ISH was negative. Subcortical areas showed patchy myelin pallor without over demyelination secondary to infiltration by the lymphoma cells.

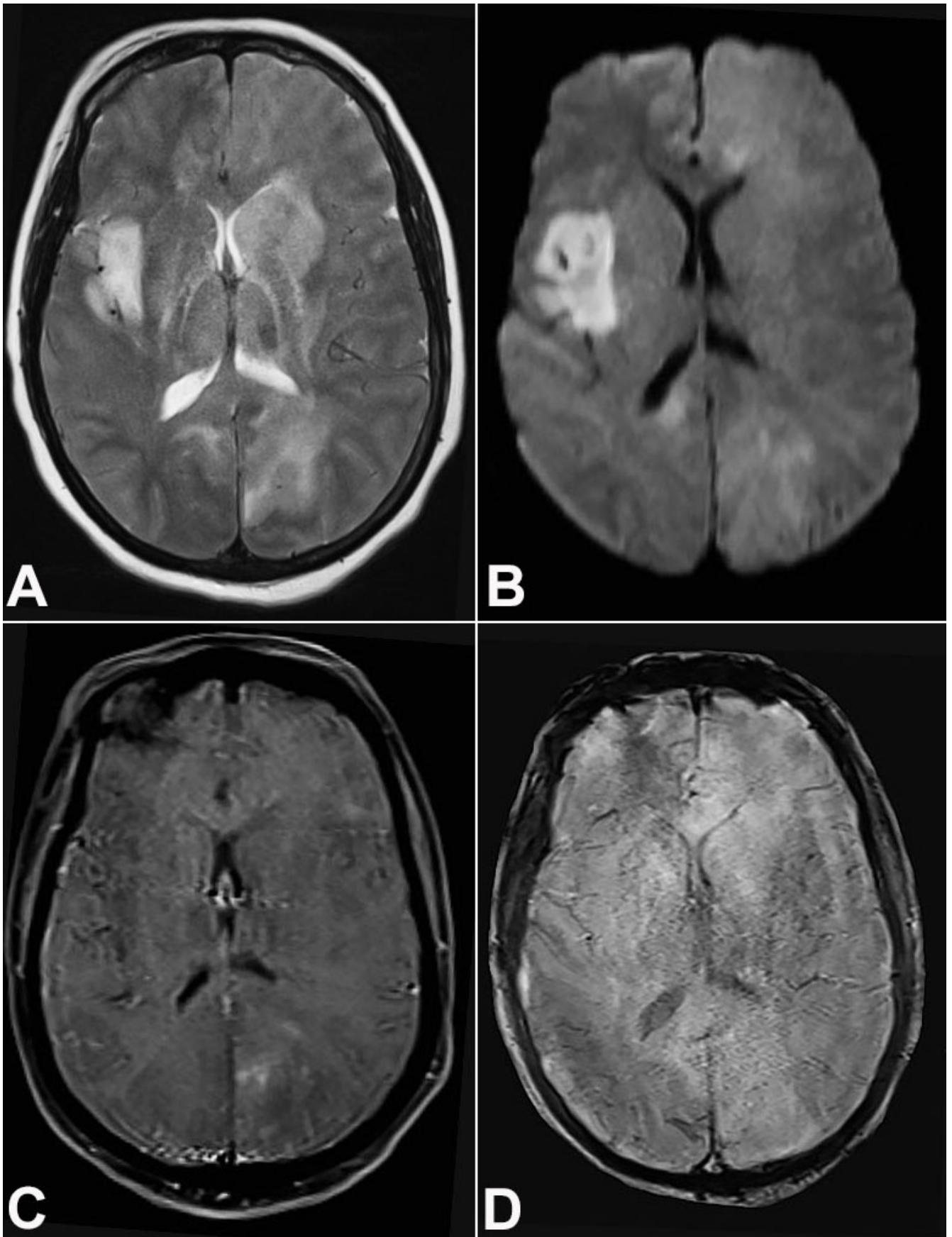


Figure 1. Brain MRI. **A** – Axial T2 weighted image shows ill-defined hyperintense signal involving bilateral basal ganglia (Left > Right), thalami, right insula, cortical and subcortical white matter in bilateral occipital lobes (Left> Right); **B** – Axial Diffusion weighted image shows areas of patchy diffusion restriction, more in the right insula; **C** – Axial T1 weighted post contrast image shows areas of mild patchy left occipital enhancement; **D** – Axial SWI image shows no evidence of hemorrhage

Table 2. laboratory work up

| Test | result | RR | Test | result | RR |
|---------------------------------|--------|------------|-----------------------|--------------|-----------|
| Hb (g/dl) | 10.9 | 12-15.5 | Ca+ (mg/dl) | 8.8 | 8.8-10.2 |
| RBC (10 ¹² /L) | 3.5 | 4.0-5.2 | PO4 (mg/dl) | 2.8 | 2.7-4.5 |
| Ht (%) | 34.2 | 36-46 | Mg+ (mg/dl) | 1.6 | 1.58-2.55 |
| RDW (%) | 18.2 | 11-14.5 | AST (U/L) | 21 | 2-40 |
| MCV | 81.6 | 80-100 | ALT (U/L) | 10 | 2-41 |
| MCHC | 32 | 31-37 | ALP (U/L) | 80 | 42-128 |
| TLC (/mm ³) | 18000 | 4000-11000 | T bil (mg/dl) | 1.2 | 0.2-1.2 |
| Plt (x10 ⁵ /m) | 2,51 | 1,5-4,5 | D bil (mg/dl) | 0.3 | 0-0.3 |
| ESR (mm - 1 st hour) | 11 | 2-20 | total protein (g/dl) | 5.7 | 6.4-8.3 |
| CRP (mg/L) | 24.69 | <10 | albumin (g/dl) | 3.3 | 3.4-4.8 |
| Creatinine (mg/dl) | 0.7 | 0.5-1.2 | uric acid (mg/dl) | 4.1 | 3.5-7.0 |
| Urea (mg/dl) | 13 | 10-50 | LDH (U/L) | 319 | 135-225 |
| Sodium (mEq/L) | 135 | 135-145 | procalcitonin (ng/ml) | 0.17 | 0.01-0.50 |
| Potassium (mEq/L) | 3.6 | 3.5-5.0 | Ammonia (μmol/L) | 44.5 | 19-71 |
| Chloride (mEq/L) | 101 | 90-107 | HbsAg/ Anti HCV/ HIV | Non-reactive | - |

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, RBC: HCT: Hematocrit, HCV: Hepatitis C virus, HbsAg: Hepatitis B surface antigen, HIV: Human immunodeficiency virus, LDH: Lactate dehydrogenase, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, Plt= platelets, RDW: Red blood cells, Red cell distribution width, TLC: Total leucocyte count, T bil: total bilirubin, D bil: direct bilirubin.

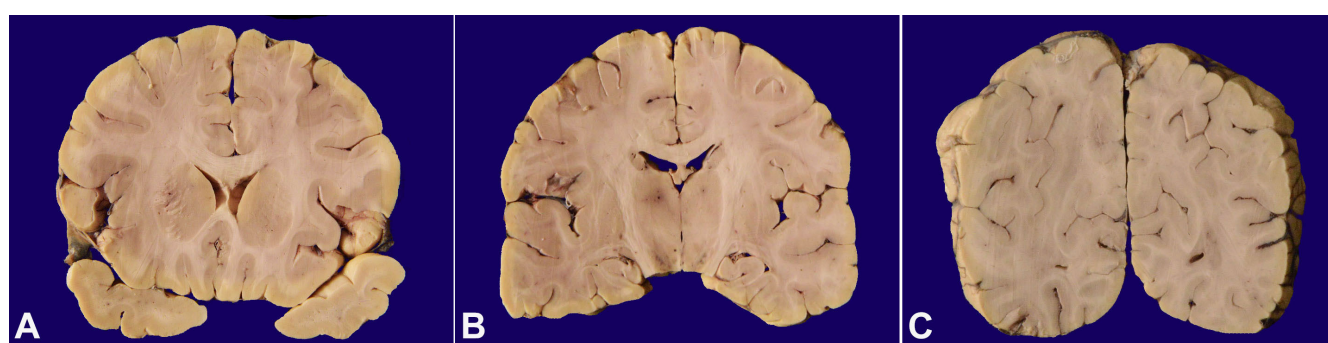


Figure 2. Gross view of the brain. **A** – Coronal section showing irregularity in left anterior limb of internal capsule extending to head of caudate; **B** – Prominence of intraparenchymal vessels in bilateral thalamus; **C** – Loss of grey-white junction noted in left striate cortex with surrounding edema.

DISCUSSION

Lymphomatosis cerebri is a rare histological pattern of PCNSL with less than 20 cases in immunocompetent patients reported as single case reports in the literature.⁴⁻¹¹ Due to its rarity, the exact incidence is not known. In majority, this pattern has been described with B cell lineage, with tumor cells expressing CD19, CD20, and CD79a, few rare examples of T cell is also on record.¹² Patients mostly present with variable clinical symptoms such as gait disturbance, focal weakness, decline of cognitive function, memory disturbance, personality

changes, dementia, anorexia, orthostatic hypotension, paraparesis, and weight loss.¹⁰ Importantly, the clinical presentation of LC is often confounded, as the symptoms like dementia and personality change are often not noticeable and attributed to increasing age. Moreover, such symptoms are easily mistaken for other more common conditions such as infectious, inflammatory, vascular, toxic, or neurodegenerative etiologies causing white-matter damage. To further complicate things, the treatment with corticosteroids gives temporary symptomatic relief and may obscure the biopsy findings.⁶ In the past two decades, an increased

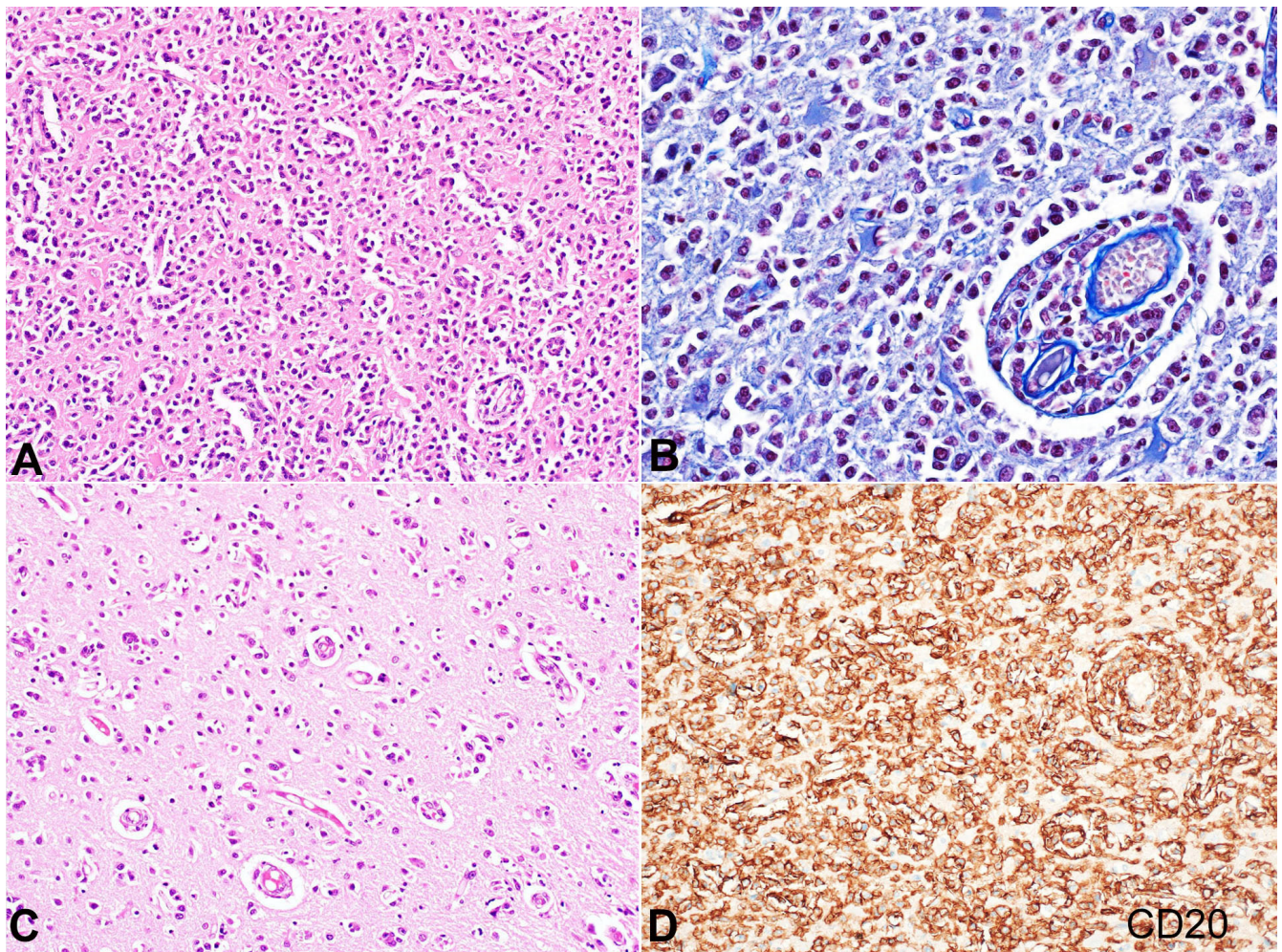


Figure 3. Photomicrographs of the brain. **A** – Low magnification of striate cortex depicting non-cohesive, atypical lymphoid cells percolating through the parenchyma (H&E x200); **B** – Focal areas showing a modest perivascular cuffing with finely dispersed lymphoma cells in adjacent parenchyma (Martius scarlet blue x400); **C** – High magnification of frontal cortex depicting fine infiltration by lymphoma cells (H&E x400); **D** – Strong diffuse immunopositivity of neoplastic cells with CD20 (immunoperoxidase x400).

incidence of PCNSL has been reported in patients older than 60 years. However, it can affect patients of any age, with a peak incidence during the fifth to seventh decades of life.¹³ Useful diagnostic histologic clues include the atypical nature of the discrete lymphoid cells, mitotic figures, and apoptotic bodies that are often deceptively admixed with the atypical cells and should be carefully searched for, especially in a stereotactic biopsy.

At gross, despite the absence of any mass-like lesions, they produce subtle changes of loss of grey-white distinction, the granularity of the parenchyma, and edema.⁵ On imaging, primary CNS lymphomas present as homogeneously enhancing periventricular or superficial lesions that are iso to hypodense on CT, iso or hypointense on T1 and hypointense to grey matter on T2.¹⁴ Lymphomatosis cerebri, on the other hand, presents as diffuse and asymmetric, abnormal

T2-hyperintensity in deep and subcortical white matter with involvement of corpus callosum. Contrast-enhancement pattern may vary from no-enhancement to patchy non-mass-like enhancement or nodular/mass-like enhancement.¹⁵ Intravascular lymphoma (IL) is an important differential diagnosis on imaging and may presents with infarct-like lesions, nonspecific diffuse white matter lesions, meningeal enhancement, or large mass-like lesions.¹⁶ It needs mention and differentiation from LC; the neoplastic cells in this entity (IL) selectively grow within the lumens of small vessels and capillaries and do not form mass lesions. This pattern is likely caused by a defect in the homing receptors in the neoplastic cells.¹⁷ Other differentials include diffuse glioma (gliomatosis cerebri), progressive multifocal leukoencephalopathy (PMLE), vasculitis, microangiopathy, and demyelination.¹⁰ The diffuse

infiltration of the brain parenchyma evident in gliomatosis is a potential diagnostic pitfall; however, immunoreactivity for glial fibrillary acidic protein (GFAP) distinguishes the former from the latter. Likewise, the splitting of argyrophilic fibers around the vessels in case of LC and PCNSL, brings vasculitis and microangiopathy amongst the differentials. The neoplastic nature of the infiltrate within the vessels helps in resolving the diagnostic dilemma. Demyelination noted in cases of PMLE typically affects the white matter anywhere within the central nervous system. It is caused due to the JC virus, the inclusions of which are evident in the oligodendrocytes as ground-glass nuclei, and reveals positivity with SV40 immunohistochemistry.¹⁸

Interestingly, studies have indicated variations in the expression of Lymphocyte Function Associated Antigen 1 (LFA-1 or CD11a, $\alpha 1\beta 2$), which may be responsible for differences in individual tumor cell permeation of the brain as these discohesive, infiltrating cells in LC have been detected to show less immunostaining for LFA-1 than did lymphoma cells within compact cell clusters.¹⁷

In conclusion, this summary features an unusual variant of PCNSL, which may often be missed on stereotactic biopsy owing to the nonspecific symptoms at presentation, the variable picture at imaging, and subtle infiltrative nature of the lesion at histology. Furthermore, despite the poor outcome, intensive treatment may be considered, especially in patients with better Karnofsky Performance Status.

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This study was carried out at Post Graduate Institute of Medical Education and Research, Chandigarh, India

Authors' contributions: Balamurugan Thirunavukkarasu assisted in autopsy analysis, critically reviewed the literature and drafted the manuscript, Kirti Gupta performed the autopsy analysis and diagnosed the case, critically reviewed the literature and drafted the manuscript. Ritu Shree managed the patient clinically, and reviewed the literature. Anuj Prabhakar performed the imaging and Radiological analysis, reviewed the literature. Aastha Takkar Kapila managed the patient clinically, reviewed the literature. Vivek Lal: managed the patient clinically, reviewed the literature. All authors proofread the final version and approved the manuscript for publication.

Ethics statement: Written informed consent was taken for the autopsy from the next of kin and the authors retain informed consent signed by the deceased's next of kin authorizing the data publication, and the manuscript is by the Institutional Ethics rules.

Conflict of interest: The authors have no conflict of interest to declare.

Financial support: The authors declare that no financial support was received.

Submitted on: December 8th, 2020

Accepted on: December 29th, 2020

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