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Ghost tumor in primary CNS lymphoma; a rare case of spontaneous regression and relapse with meningeal disseminate

Mohammad Amin Najafi[1#], Ali Alavi[2#], Zahra Masoumi[3], Raavi Gupta[4], Parto Nasri[5*]

[1]Department of Neurology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Pathology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA
[3]Department of Neurology, Isfahan Neurosciences Research Center, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Pathology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA
[5]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[#] These authors contributed equally to this work.

***Correspondence to**
Parto Nasri, Email: parto.nasri@gmail.com

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive subtype of non-Hodgkin lymphoma confined to the central nervous system (CNS). An exceptionally rare phenomenon known as a "ghost tumor" involves the spontaneous regression of CNS lesions, followed by recurrence without any treatment. This presents significant diagnostic challenges and may delay appropriate management. Here, we report a rare case of PCNSL with initial spontaneous regression and subsequent relapse as meningeal dissemination. A 71-year-old woman presented in February 2024 with progressive memory loss, gait instability, and urinary incontinence. She had experienced nonspecific neurological symptoms three years earlier, during which brain MRI revealed two enhancing periventricular lesions that resolved spontaneously without corticosteroids or specific therapy. A new MRI revealed a communicating hydrocephalus. Following lumbar puncture and CSF drainage, the patient showed significant clinical improvement. Flow cytometry and cytological analysis of the CSF confirmed B-cell lymphoma with a dominant, near-pure CD5-negative clonal B cell population. A comprehensive systemic evaluation ruled out extracranial involvement, establishing the diagnosis of primary CNS lymphoma with meningeal dissemination. This case illustrates an unusual clinical course of PCNSL with spontaneous tumor regression and delayed meningeal relapse, leading to hydrocephalus. Clinicians should consider PCNSL in the differential diagnosis of unexplained CNS lesions, even in the setting of spontaneous regression, and pursue long-term monitoring of patients.

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Introduction

The "ghost tumor" phenomenon refers to an intracranial mass lesion that spontaneously disappears or markedly shrinks on neuroimaging before a definitive diagnosis or treatment is established (in the absence of steroid therapy) (1). Such vanishing tumors have been reported in various central nervous system (CNS) pathologies. Notably, primary central nervous system lymphoma (PCNSL) is often implicated as a cause in many cases (2). In fact, the remarkable steroid sensitivity of PCNSL has historically earned it the moniker of a "ghost" or "vanishing" tumor in the neuro-oncology literature. However, similar transient regressions have occasionally been observed with other lesions (e.g., certain demyelinating pseudotumors or germ cell tumors); therefore, a vanishing lesion is not pathognomonic for lymphoma (3). In PCNSL, transient tumor regression is frequently triggered by corticosteroid administration, with up to ~50% of PCNSL lesions showing dramatic radiologic improvement after steroid treatment (4). This effect can induce a striking but temporary remission of enhancing lesions, often complicating diagnosis; if biopsy is attempted post-steroid, it may yield only necrosis or inflammatory cells instead of a viable tumor (4). Spontaneous remission of PCNSL without any treatment (i.e., not attributable to steroids or other therapies) has also been documented, but this phenomenon is exceedingly rare, with only isolated case reports in the literature (3). Such cases demonstrate that PCNSL can occasionally regress on its own, although this remission is typically temporary rather than curative (3). The ghost tumor phenomenon poses significant diagnostic challenges. When a suspected CNS lymphoma lesion regresses or vanishes prior to biopsy, histopathological

Key point

- Primary CNS lymphoma can present as a ghost tumor, with spontaneous regression followed by relapse and meningeal dissemination.
- Spontaneous regression of CNS lesions does not rule out underlying malignancies, and clinicians should avoid a 'wait-and-see' approach in patients with unexplained CNS lesions.

confirmation becomes difficult, and initial biopsies often turn out to be nondiagnostic or falsely negative (5). Furthermore, if an intracranial tumor has spontaneously regressed, vigilant long-term follow-up is imperative, as the lesion will often reappear within months, allowing a definitive pathological diagnosis upon re-biopsy (6).

Case Presentation

A 71-year-old woman with a history of significant unintentional weight loss over the past year presented with progressive memory loss, instability, and urinary incontinence for 5 months. Neurological examination revealed impaired upward gaze, dysarthria, and severe gait instability, rendering the patient unable to sit or stand without assistance. Cognitive assessment indicated confusion and speech difficulties.

Family members reported a history of dizziness 4 years prior (2019). Magnetic resonance imaging at that time revealed two periventricular and infratentorial lesions that appeared hyperintense on T2-weighted and FLAIR sequences and showed homogeneous enhancement following gadolinium administration (Figure 1).

The patient declined a stereotactic brain biopsy in 2019 and abandoned further treatment. She sought symptomatic relief through conventional medical treatments, including antihistamines for dizziness, and engaged in complementary traditional therapies such as herbal supplements and acupuncture. Over the following months, the patient's symptoms improved, and follow-up

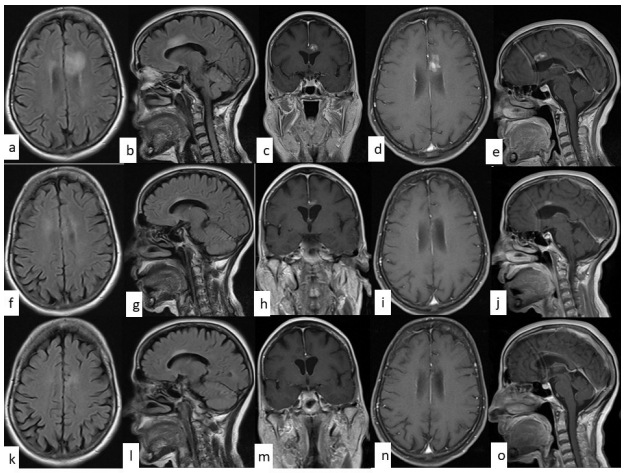

Figure 2. Follow-up MRIs demonstrating gradual regression of lesions. December 2019: Periventricular lesion with high intensity in FLAIR (a, b) and homogeneous enhancement on GAD-enhanced T1W images (c–e); decreased enhancement compared with previous scan. August 2020: Subtle periventricular FLAIR hyperintensity (f, g) with mild enhancement on GAD-enhanced T1W images (h–j); marked regression of lesion. June 2022: Subtle periventricular FLAIR hyperintensity (k, l) without enhancement on GAD-enhanced T1W images (m–o); near-complete regression.

MRI showed near-complete resolution of the previously noted lesions, with only faint residual hyperintensity on T2-weighted and FLAIR images and no contrast enhancement (Figure 2).

Given the clinical improvement and radiological regression, no further interventions were performed, and the patient was advised to return if symptoms recurred.

A new brain MRI was performed for the patient, which demonstrated marked communicating hydrocephalus (Figure 3).

Given the progressive neurological decline and imaging findings, a lumbar puncture (LP) was performed, and 50 cc of cerebrospinal fluid (CSF) was drained for three consecutive days. The patient's symptoms improved

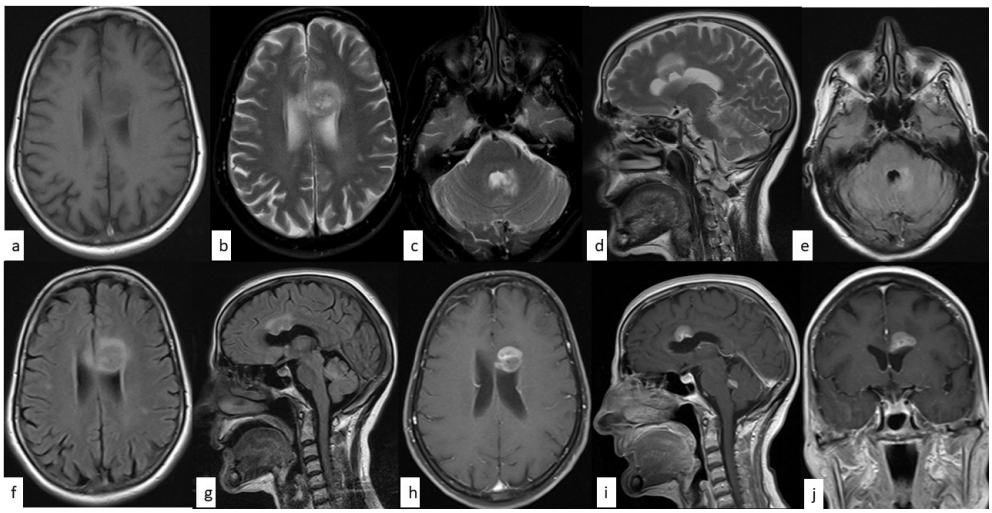

Figure 1. Initial brain MRI in (May 2019), demonstrating two periventricular lesions (supratentorial and infratentorial) with low T1 signal intensity (a) and high T2/FLAIR signal intensities (b-g). Gadolinium-enhanced T1W images showing homogenous enhancement (h-j).

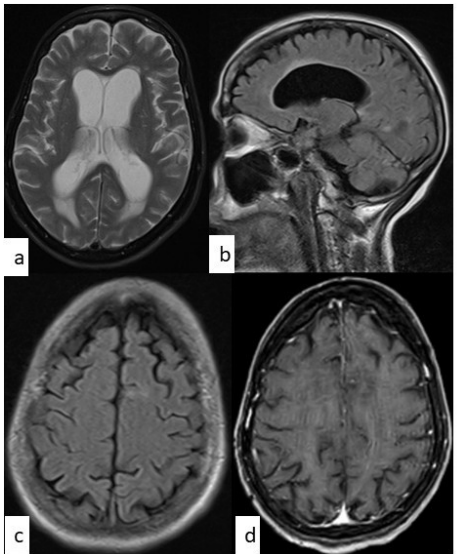

Figure 3. Brain MRI at presentation showing communicating hydrocephalus with interstitial edema on axial T2W image (a); subtle periventricular FLAIR hyperintensity (b, c); no enhancement on GAD-enhanced T1W image (d).

dramatically, and she could sit and walk with assistance. The patient's cognitive and speech abilities improved. CSF analysis revealed an elevated white blood cell count of 120 cells/mm³ with 70% lymphocytes, elevated protein levels (94 mg/dL) (normal range: 30-45 mg/dl), and decreased glucose levels (29 mg/dL). Microbiological studies, including bacterial cultures, viral PCR panels, and fungal stains, were performed on the CSF, and all results were negative. Cytological assessment revealed atypical lymphoid cells with high nuclear-to-cytoplasmic ratios and prominent nucleoli (Figure 4).

Flow cytometric immunophenotyping confirmed leptomeningeal infiltration by a clonal B-cell population. Using forward and side scatter gating (R1), small, low-complexity lymphocytes were isolated, of which 93.9% were in quadrant 1 ($CD19^+/CD5^-$), with only 1.4% co-expressing CD5, indicating the predominance of CD5-negative B cells. Dual-parameter plots of CD19 versus CD45 confirmed that 95.6% of gated cells were brightly $CD19^+/CD45^+$, with no CD45-dim subset present. The corresponding single-parameter histograms showed strong unimodal peaks for CD19 (orange) and CD45 (red), whereas CD5 expression (green) was minimal, displaying only a minor background (~16%) consistent with residual T cells. Altogether, the data demonstrated a highly homogenous $CD19^+/CD5^-/CD45^+$ population accounting for over 90% of nucleated CSF cells, providing strong evidence of leptomeningeal spread of the patient's CD5-negative primary CNS B-cell lymphoma (Figure 5).

Discussion

Primary CNS lymphoma is a rare form of extranodal non-Hodgkin lymphoma that is typically confined to the brain, eyes, and CSF without evidence of systemic spread. The incidence of meningeal dissemination in primary CNS lymphoma is unknown. Meningeal dissemination has been reported in 7%–42% of patients with PCNSL, typically diagnosed through morphologic CSF assessment, which is considered the gold standard for detecting meningeal dissemination in malignant diseases. Here, we present a case of meningeal dissemination of PCNSL in which the parenchymal lesion regressed within 3 years, and the lymphoma presented after three years with symptoms secondary to hydrocephalus due to meningeal dissemination. This case illustrates the diagnostic complexities of PCNSL, particularly when it presents as a ghost tumor with spontaneous regression and recurrence of CNS lesions. The spontaneous regression of PCNSL lesions without corticosteroid treatment, as observed in

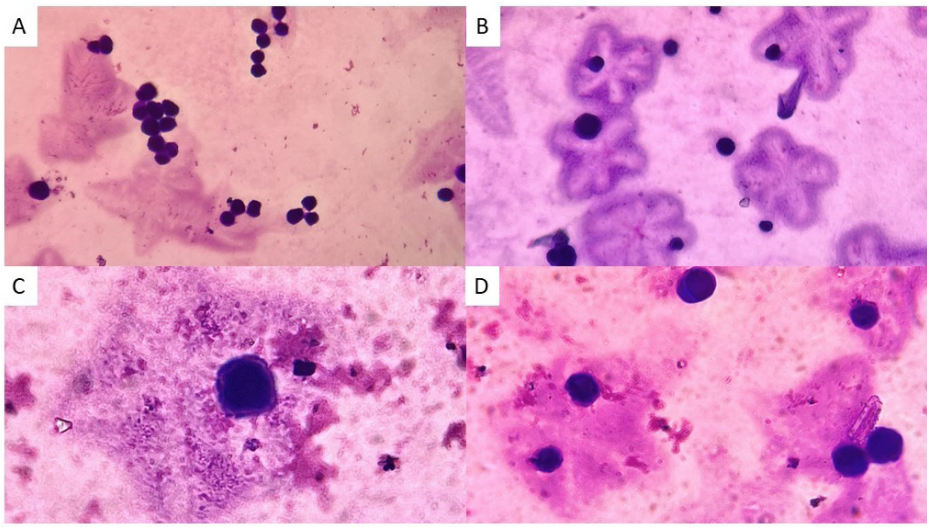

Figure 4. Cytological examination of cerebrospinal fluid (Papanicolaou stain). Low-power view (×200) showing atypical and normal lymphocytes (A, B); atypical cells approximately 2–3 times larger than normal lymphocytes. High-power view (×400) showing atypical lymphocytes with high nuclear-to-cytoplasmic ratio, irregular nuclear borders, and hyperchromatic nuclei (C, D).

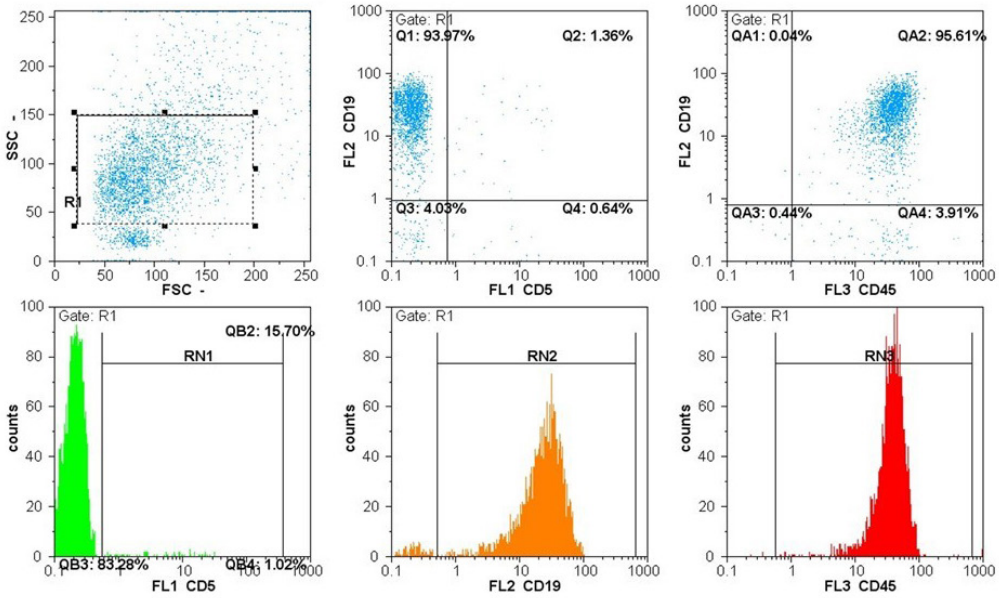

Figure 5. Flow cytometry of cerebrospinal fluid (CSF) showing dominant clonal B-cell population. Lymphocytes gated in R1: 94% $CD19^{+}/CD5^{-}$ and 96% $CD19^{+}/CD45^{+}$ with bright, unimodal CD19 and CD45 histograms and minimal CD5 signal. Findings consistent with near-pure CD5-negative B-cell infiltration, indicating leptomeningeal spread of primary CNS lymphoma. Systemic evaluation (whole-body PET-CT, CAP-CT, bone marrow biopsy, abdominal ultrasound) showing no extracranial disease; diagnosis of meningeal dissemination of primary CNS lymphoma confirmed.

this patient, is exceptionally rare and adds to diagnostic ambiguity. The absence of corticosteroid use in this case eliminates steroid-induced tumor regression, a well-documented phenomenon in PCNSL that can complicate diagnosis by masking the lesions (7). This emphasizes that spontaneous lesion regression does not exclude malignancy and that reliance on imaging alone may lead to false reassurance.

Several hypotheses have been proposed to explain spontaneous tumor regression, including immune-mediated mechanisms, tumor ischemia, apoptosis, and hormonal influences (8). In the context of PCNSL, an enhanced immune response may temporarily suppress tumor growth, leading to transient regression of the lesion. However, immune control is often incomplete or temporary, allowing for eventual tumor recurrence and progression (1). Differentiating PCNSL from other CNS pathologies is challenging because of overlapping clinical and radiological features. Demyelinating diseases, such as multiple sclerosis, can present with periventricular lesions and transient neurological symptoms. However, the patient's age and MRI findings are more characteristic of PCNSL (7,9). Infectious processes, such as viral encephalitis or bacterial abscesses, may also mimic these findings but are typically associated with systemic symptoms and CSF findings indicative of infection.

Conclusion

This case highlights the rare presentation of PCNSL as a ghost tumor, relapsing with meningeal dissemination symptoms, emphasizing that spontaneous regression of CNS lesions does not exclude underlying malignancies. Clinicians should be cautious when adopting a 'wait-and-see' approach in patients with unexplained CNS lesions, even when initial symptoms resolve, and imaging findings improve. Regular follow-up with MRI and consideration of early diagnostic interventions are essential to prevent delayed diagnosis and improve patient outcomes.

Authors' contribution

Conceptualization: Mohammad Amin Najafi.
Data curation: Parto Nasri, Mohammad Amin Najafi.
Formal analysis: Parto Nasri, Ali Alavi, Zahra Masoumi.
Investigation: Mohammad Amin Najafi, Raavi Gupta.
Methodology: Mohammad Amin Najafi, Parto Nasri, Ali Alavi.
Project administration: Mohammad Amin Najafi, Raavi Gupta.
Resources: Parto Nasri, Zahra Masoumi.
Software: Parto Nasri, Zahra Masoumi.
Supervision: Mohammad Amin Najafi, Raavi Gupta.
Validation: Mohammad Amin Najafi, Raavi Gupta.
Visualization: Mohammad Amin Najafi, Parto Nasri, Zahra Masoumi, Ali Alavi.
Writing–original draft: Mohammad Amin Najafi, Ali Alavi.
Writing–review & editing: Parto Nasri, Zahra Masoumi, Mohammad Amin Najafi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient has provided written informed consent for publication as a case report. Additionally, ethical issues, including plagiarism, data fabrication, and double publication, have been strictly observed by the authors.

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References

1. Okita Y, Narita Y, Miyakita Y, Ohno M, Fukushima S, Maeshima A, et al. Long-term follow-up of vanishing tumors in the brain: how should a lesion mimicking primary CNS lymphoma be managed? Clin Neurol Neurosurg. 2012;114:1217-21. doi: 10.1016/j.clineuro.2012.02.053.
2. Frassanito P, Tamburrini G, Massimi L, Caldarelli M, Di Rocco C. Ghost Tumors of the Central Nervous System: Definition, Clinical Implications, and Proposal of Classification. World Neurosurg. 2015;84:663-70. doi: 10.1016/j.wneu.2015.03.063.
3. Debonera F, Nasta S, Martinez-Lage M, Schuster SJ, Tsai DE. Primary diffuse large B-cell lymphoma of the CNS: a rare case of spontaneous remission. Int J Hematol Oncol. 2017;6:69-73. doi: 10.2217/ijh-2017-0009.
4. Scheichel F, Pinggera D, Popadic B, Sherif C, Marhold F, Freyschlag CF. An Update on Neurosurgical Management of Primary CNS Lymphoma in Immunocompetent Patients. Front Oncol. 2022;12:884724. doi: 10.3389/fonc.2022.884724.
5. Bromberg JE, Siemers MD, Taphoorn MJ. Is a "vanishing tumor" always a lymphoma? Neurology. 2002;59:762-4. doi: 10.1212/wnl.59.5.762.
6. Al-Yamany M, Lozano A, Nag S, Laperriere N, Bernstein M. Spontaneous remission of primary central nervous system lymphoma: report of 3 cases and discussion of pathophysiology. J Neurooncol. 1999;42:151-9. doi: 10.1023/a:1006162615774.
7. Batchelor T, Loeffler JS. Primary CNS lymphoma. J Clin Oncol. 2006;24:1281-8. doi: 10.1200/JCO.2005.04.8819.
8. Papac RJ. Spontaneous regression of cancer: possible mechanisms. In Vivo. 1998;12:571-8.
9. Grommes C, DeAngelis LM. Primary CNS Lymphoma. J Clin Oncol. 2017;35:2410-2418. doi: 10.1200/JCO.2017.72.7602.