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Case Report

Concurrent Neurological Involvement in Chronic Lymphocytic Leukemia: A Rare Case With Brain and Spinal Manifestations

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ABSTRACT

Background and Importance: Chronic lymphocytic leukemia (CLL) stands as the predominant form of lymphoproliferative ailment in America. Despite its rarity, CLL invasion into the central nervous system (CNS) is known to have varied consequences. Furthermore, it is an exceptional occurrence for symptomatic CNS lesions to serve as a foremost indication of undiagnosed CLL.

Case Presentation: In this case study, a 71-year-old male patient with CLL medical history presented to our center due to CNS involvement and symptoms of headache and weakness in the lower extremities. Subsequent magnetic resonance imaging (MRI) evaluation identified a “ring or target sign” in both the temporal lobe and intramedullary spinal cord at the T9-T10 level. A surgical procedure was performed for resection of the temporal lesion, which histologically confirmed CLL.

Conclusion: To conclude, the initial manifestation of CNS involvement in chronic lymphocytic leukemia is rare and not biased toward any specific demographic factors, such as age, gender, or ethnicity. Such occurrence can take place at any stage of CLL. Thus, it is crucial to consider this likelihood when patients with a prior history of CLL show neurological symptoms.

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Highlights

- Primary central nervous system (CNS) involvement in chronic lymphocytic leukemia (CLL)
- Mechanisms and imaging features of CNS involvement in CLL
- Treatment of CNS involvement in CLL

Plain Language Summary

In this report, we explore a rare occurrence of chronic lymphocytic leukemia (CLL), a type of blood cancer. While CLL usually affects the blood and bone marrow, our study focuses on cases that unexpectedly involve the central nervous system (CNS), a rare and serious complication. Our results shed light on the unusual CNS involvement in CLL, highlighting the importance of early detection and management to address the range of neurological symptoms CLL patients may experience. This report serves as a valuable resource for both medical professionals and those interested in understanding the complexities of CLL and its potential impact on the nervous system

1. Background and Importance

Chronic lymphocytic leukemia (CLL) is a neoplastic proliferation of mature B-cells that primarily involves the blood and bone marrow. However, extramedullary involvement, including central nervous system (CNS) infiltration, can occur in up to 4%-5% of patients with CLL with various types of manifestation [1]. Patients with CLL may experience a range of neurological symptoms that can vary in severity from mild to severe. These symptoms include cognitive impairment, such as memory loss and difficulty concentrating, peripheral neuropathy which can cause tingling or numbness in extremities, cerebellar ataxia which impacts coordination and balance, depression, anxiety, fatigue, and sleep disturbances [2]. In this study, we describe a CLL case with rare CNS involvement and review up-to-date literature about this issue.

2. Case Presentation

A 71-year-old man with a headache and progressive lower extremity weakness was referred to the neurosurgical department of the Mashhad University of Medical School. The medical history revealed hypertension, and diagnosed with CLL 1.5 months ago. The drug history showed a prescription for aspirin.

Neurologic examination demonstrated a Glasgow Coma scale (GCS) of 15 with normal pupil size. Examination of all cranial nerves was normal. Lower extremities forces were 4 out of 5. and plantar reflexes were flat for both feet with decreased DTR, but no sensory dysfunction was found.

The patients underwent magnetic resonance imaging (MRI) which revealed a “ring or target sign” in the right temporal lobe and similar round shape intramedullary lesion enhanced by gadolinium in T1 according to T10 - T11 (Figure 1). Before and after the surgery, the patient received dexamethasone (0.4 to 0.8 mg/kg/day), a type of corticosteroid, to help manage symptoms, such as inflammation and swelling in the brain. With high suspicion of metastatic origin, the patient underwent temporal lobe metastasis resection.

The imaging findings on MRI, specifically the “ring or target sign” in the right temporal lobe and the intramedullary lesion in the spinal cord raised concern for CNS infiltration. While CNS involvement can be detected through cerebrospinal fluid (CSF) analysis, a brain biopsy is often considered to make a definitive diagnosis and to rule out other potential differential diagnoses. Given the presence of a newly diagnosed CLL and the appearance of the lesions on imaging, a high suspicion was found that these CNS lesions were related to metastatic CLL involvement. The patient presented with neurological symptoms, including headache and lower extremity weakness. The surgical intervention was conducted to address these symptoms by removing the tumor mass and reducing pressure on the surrounding brain tissue and spinal cord.

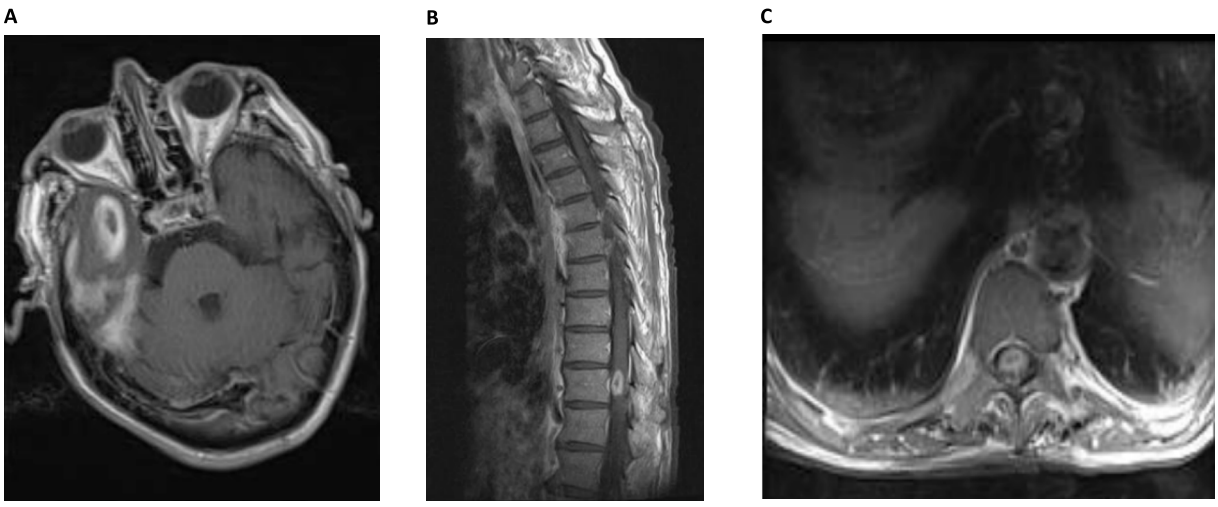

Figure 1. Different sequences of magnetic resonance imaging (MRI) finding in chronic lymphocytic leukemia (CLL) patient, A. T1 with GAD axial view of brain MRI, C. T1 with GAD sagittal dorsal view of spine with open ring sign in T9-T10, D. T1 with GAD axial view of spine with open ring sign in T9-T10

The indication for surgery in this known case of CLL with CNS involvement lies in the severity of neurological symptoms and the need for a definitive diagnosis. Even though CLL is a hematologic disease, CNS involvement can lead to various neurological complications, including headaches, weakness, and cognitive impairments. In such cases, prompt intervention is essential to address the immediate neurological issues and potentially improve the patient's quality of life. While CLL may be diagnosed based on specific markers and blood tests, the presence of CNS involvement adds complexity and requires more targeted management. Surgical intervention can aid in obtaining a tissue sample for accurate diagnosis, as imaging findings alone may not be sufficient to confirm the nature of the lesions. Additionally, surgery can offer symptomatic relief and pave the way for further treatment, such as chemotherapy or radiotherapy, to target the underlying CLL.

The pathological result revealed tumor infiltration of the brain in the background of CLL (Figure 2). The mass was removed and pathology demonstrated disseminated large B-cell lymphoma of non-germinal center type according to Hans' classification. Table 1

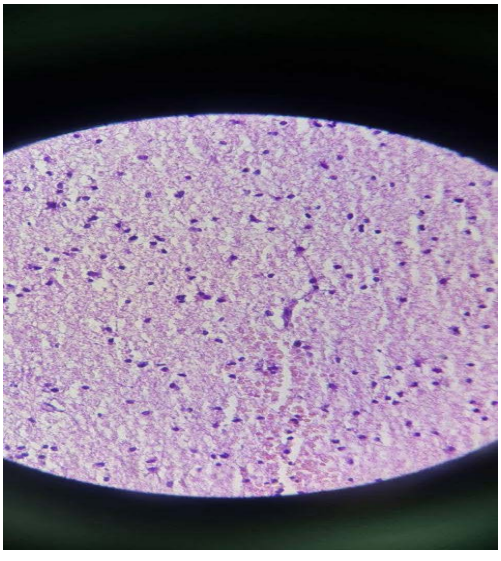

Figure 2. Pathologic Study of Chronic Lymphocytic Leukemia (CLL) Patient

A diffuse large B-cell with non-germinal center type is seen.

Table 1. Hematologic assessment of patient

Parameters	Value	Parameters	Value
White blood Cells/µL	12.1×10^9	Na	140 mEq/L
Neutrophils	15%	K	4.1 mEq/L
Basophils	2%	Cl	90 mEq/L
Eosinophils	6.1%	BUN	10 mg/dL
Lymphocytes	76.9%	Cr	0.9 mg/dL
Monocytes	0		
Others	0	Alb	4.0 g/dL
Platelets	25.0×10^4/µL	AST	23 U/L
Red Blood Count	400×10^4/µL	ALT	30 U/L
Hemoglobin	10.0 g/dL	Total bilirubin	0.3 mg/dL
Hematocrit	41.1%	Direct bilirubin	0.1 mg/dL
MCV	92.3 fL	ALP	448 U/L
MCH	25.1 pg	γGTP	85 U/L
MCHC	25.3 g/dL	LDH	259 U/L
APTT	25.0 s	CRP	0.031 mg/dL
PT	132%		
FBG	240 mg/dL	IgG	560 mg/dL
AT-III	109%	IgA	60 mg/dL
HBs-Ag	—	IgM	26 mg/dL
HCV-Ab	—	sIL2R	10.000 U/mL
HTLV-1	—	BMG	2.0 mg/L
HIV	—	ANA	—

Abbreviations: MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; APTT: activated partial thromboplastin time; PT: prothrombin time; FBG: fasting blood glucose; AT-III: antithrombin III; HBs-Ag: hepatitis B virus surface antigen; HCV-Ab: hepatitis C antibody; HTLV-1: human T-lymphotropic virus type 1; HIV: human immunodeficiency virus; Na: sodium; BUN: blood urea nitrogen; K: potassium; Cl: Chloride; Cr: chromium; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; γGTP: gamma glutamyl transpeptidase; LDH: lactate dehydrogenase; CRP: C-reactive protein; IgG: immunoglobulin G; sIL2R: soluble interleukin 2 receptor; BMG: buried-metal-grid; ANA: anti-nuclear antibody

presents the hematologic assessment of the patient. The leukocyte count was 12.1×10^9/L (76.9% lymphocytes), and fluorescence-activated cell sorting analysis of blood revealed a clonal B-cell population (36.75% leukocytes) corresponding to the immunological chronic Myelogenous Leukemia (CML) profile. Bone marrow aspiration and biopsy also indicated CLL. Furthermore, the patient underwent chemotherapy. Two months after surgery, lower extremities forces were completely intact and referred to an oncologist for further treatment.

Table 2. Case-studies about central nervous system (CNS) involvement of chronic lymphocytic leukemia (CLL)

Study	Year	Sex	Stage of CLL	Symptoms	MRI Finding		Treatment
					Brain	Spinal	
Otani et al. [9]	2018	Female	N/A	Progressive mental disturbance	Ring sign in bi-frontal lobes	-	Chemotharpy
Akdogan et al. [10]	2020	Male	N/A	Incontinency		T1-T4 enhancements	Prednisolone +chemotharpy
Quitt et al. [11]	1994	Female	N/A	Loss of connection	Brain stem	-	-
Nakanishi et al. [12]	2020	Male	3 months	Diplopia	Right temporal lobe	-	Refused to treamtent
Albakr et al. [13]	2018	Female	Onset	Left upper extremities weakness	Posterior fossa mass	-	Surgery+ chemotherapy
Benjamini et al. [14]	2013	Female	Onset	Double vision	Bilateral retro-orbit involvements	-	Endoscopic surgery+ chemotharpy

Abbreviations: CLL: chronic lymphocytic leukemia; MRI: magnetic resonance imaging

3. Discussion

We presented newly diagnosed CLL in a 71-year-old man complaining of headache and weakness of lower extremities forces. Although between 0.8% to 2% of CLL patients demonstrate CNS involvement, a concurrent presentation of brain and spinal invasion is rare and about 0.4%-2% [3]. CNS lesions are a completely rare consequence with no correlation to risk factors, such as age, gender, and ethnicity [4]. Moreover, the duration of the disease and Rai stage at the time of diagnosis are not related to CNS invasion [4].

Bayliss et al. reported a 78-year-old case of CLL referred with confusion and a metastatic lesion of the right temporal lobe [5]. As demonstrated in Table 2, the temporal lobe involvement appears to be rare and many studies reported a parenchymal lesion in the occipital lobe, frontal, and basal ganglia [6]. Our patient complained of headache and lower extremity weakness. Although the clinical manifestation of CNS involvement is heterogeneous, reports indicate most symptoms in patients were headache, cranial nerves palsy, and vertigo [7].

We think that the surgical procedure performed on the patient was effective in several aspects. The brain biopsy and removal of the tumor mass allowed for a definitive diagnosis of disseminated large B-cell lymphoma of the non-germinal center type in the background of CLL. This information was crucial in tailoring the subsequent treatment plan. The surgery was conducted to alleviate the patient's neurological symptoms, including headache and lower extremity weakness. By removing the tumor mass, pressure on the surrounding brain tissue and spinal cord was reduced, leading to an improvement in the patient's condition. With a confirmed diagnosis, the patient can undergo chemotherapy targeted at treating both CLL and CNS involvement. The surgical intervention was a crucial step in the comprehensive treatment plan for the patient.

The mechanisms of leukemic infiltration in CNS are poorly understood. However, disseminating can be reached by one of three means. First, transmigration across perforating cerebral vessels into the subarachnoid space, second direct extension from seeded meninges into the CSF (especially via the ependymal lining and the choroid plexus), and third, via perineural sheaths on cranial and spinal nerve roots [8].

An open ring sign was found in both the temporal and spinal cord of our patient. Otani et al. reported an open ring sign in the bilateral frontal lobe as well [9]. In addition, Akdogan reported newly onset incontinency and upper motor neuron symptoms with T1-T4 spinal enhancement transverse myelitis which further evaluation confirmed with CLL [10]. Furthermore, the final diagnosis is confirmed by brain biopsy and ruling out other differential diagnosis. Moreover, CSF analysis by lumbar puncture may indicate tumor cells, although flow cytometry may be needed to verify the results. The confirmation of our case was based on the imaging and open craniectomy. In Table 2, we described important case studies about CNS involvement in CLL. No consensus and standard regiments exist for a complete cure for CNS leukemia. The treatment is based on a combination of sur-

gery, chemotherapy, and radiotherapy. Chemotherapy is also applied in systemic or intrathecal manners.

As with any medical decision, the indication for surgery in cases of CLL with CNS involvement should be carefully evaluated individually. Each patient's clinical presentation, extent of CNS involvement, overall health status, and response to initial treatments should be considered.

Surgery may be recommended in cases where CNS involvement is suspected and the presence of neurological symptoms requires immediate attention. Additionally, when imaging findings alone are inconclusive or when a definitive diagnosis is needed, a brain biopsy through surgical intervention may be warranted.

However, healthcare providers must work collaboratively in a multidisciplinary team, including neurosurgeons, hematologists, and oncologists, to make well-informed decisions regarding the best course of action for each patient. Treatment plans should be tailored to the individual's unique circumstances and overall treatment goals

4. Conclusion

In conclusion, CLL with CNS involvement as a primary presentation is a rare clinical manifestation. Although CNS involvement has no specific age, sex, or ethnicity factors and could appear at any stage, this situation should be noted when a patient with a history of CLL demonstrates neurological symptoms. In addition, other differential diagnoses based on imaging findings of both the brain and spine should be in the context. Despite various types of treatment, combination surgical and following chemotherapy is advised in CNS involvement. However, further precise treatment protocols and chemotherapy regiments in this regard are needed.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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