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# Central Nervous System Involvement in Chronic Lymphocytic Leukemia with Characteristic Radiological Findings: Case Presentation and Review of Literature

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## Abstract

**Background**: Chronic lymphocytic leukemia is one of the most common hematological malignancies in adults. Even though this disease invades various organs, central nervous system involvement is rare. We describe intracranial invasion with characteristic radiological findings.

**Case presentation:** A 74-year-old male underwent a medical checkup, and magnetic resonance imaging of the brain showed an evenly enhanced diffuse hypertrophic dura mater. He had been diagnosed with chronic lymphocytic leukemia 11 years previously, had received chemotherapy, and was in remission. Even though he had no symptoms, dural biopsy was performed during craniotomy to make a definitive diagnosis and plan treatment. Histopathological examination suggested a dural invasion by chronic lymphocytic leukemia. We consulted a hematologist and decided on chemotherapy with ibrutinib, which has good central nervous system migration.

**Conclusion:** Asymptomatic dural invasion may be present in patients with chronic lymphocytic leukemia, and screening with magnetic resonance imaging is useful for diagnosis.

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## Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common hematological malignancies in adults. Prognosis of CLL is stage-dependent (Rai stage). In the early stage of the disease, patients have a good prognosis and a median survival of more than 10 years, whereas in more advanced stages, the prognosis is worse, and they have an expected survival of approximately 2 years [1]. CLL is known to invade various organs. Because of the development of treatment and prolonged survival, cases of invasion to other organs have increased in frequency [2]. We describe a case of intracranial invasion by CLL with characteristic radiological findings.

## Case Report

A 74-year-old man underwent a medical checkup, and magnetic resonance imaging (MRI) of the brain showed an abnormal pattern; therefore, he was referred to our department. His consciousness was clear, and he had no neurological deficit or any symptoms or signs of increased intracranial pressure such as headache or vomiting. He had been diagnosed with CLL 11 years previously, and he had received chemotherapy with fludarabine, cyclophosphamide, and ofatumumab. He remains in remission and has been followed without treatment for 5 years. Since the diagnosis of CLL, he has not experienced any symptoms with neurological signs.

MRI of the head revealed a diffuse hypertrophic dura mater. The dura was enhanced evenly, and there was a mass at the lateral midline. There were no abnormal signals in the white matter (Figure 1). The lumbar puncture demonstrated slightly turbid cerebrospinal fluid (CSF) with high protein (184 mg/dL), low glucose (49 mg/dL), and high monocyte (108/mm$^3$) levels. Cytological examination of the CSF showed atypical lymphocytes with well-stained nuclear body and cytoplasm on May-Grünwald-Giemsa stain (Figure 2a).

Even though he had no symptoms, dural biopsy was performed during craniotomy to make a definitive diagnosis and plan treatment. We collected a sample from the left frontal dura. Macroscopically, the medial side of the dura (that is, the arachnoid side) was well-vascularized and had a red coloration (Figure 2b). We applied a periosteal patch to the dural defect.

## Discussion

Although CLL is one of the most common hematological malignancies, the etiology of CLL is yet unknown. CLL mainly affects male patients who are older than 60 years at diagnosis. In the early stage of the disease, patients often are asymptomatic. In Europe and the United States, 20% to 30% of leukemia cases are CLL, compared to only 2% to 2.5% in Japan. One of the characteristics of CLL is that its frequency varies by race [3].

Even though CLL is known to invade various organs, such as peripheral blood, bone marrow, lymph nodes, spleen, and liver, involvement of the CNS associated with CLL is rare [4]. Meningeal involvement by malignant cells often occurs in cases of acute lymphocyte leukemia or malignant lymphoma [5], with frequencies of 33% [6] and 19% [7], respectively. Among cases of CNS involvement associated with CLL, meningeal involvement is much rarer, and in many cases, it forms a mass [8].

Headache, cranial nerve dysfunction, and ataxia are relatively frequent presenting symptoms and signs of CNS involvement in patients with CLL [9]. However, few patients are diagnosed with CNS involvement due to these symptoms. Most patients are asymptomatic,

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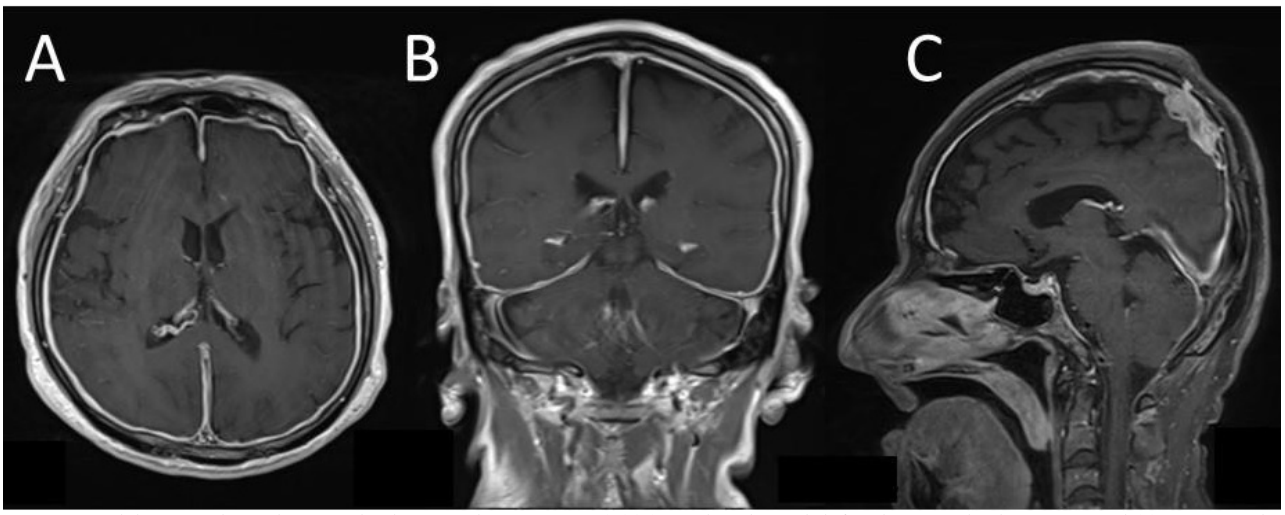


Figure 1: Gadolinium-enhanced T1-weighted images demonstrating (A)(B) evenly enhanced diffuse hypertrophicdura mater and (c) a mass at the lateral midline.

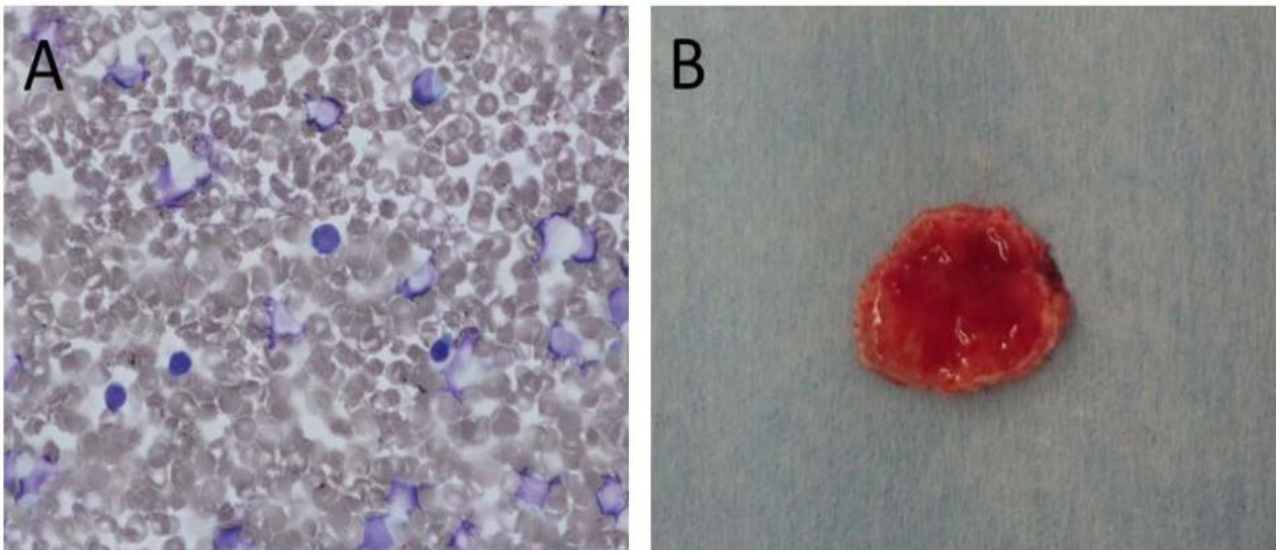


Figure 2: (A) Cytological examination showing a typical lymphocytes with well-stained nuclear body and cytoplasam(May-Grunwald-Giemsa, × 200). (B) The medial side of the dura was well-vascularized and had a red coloration

and the disease is diagnosed incidentally by neuroimaging, as in our case. According to a study by Morrison, although more than 200,000 cases of CLL have been reported in the last 20 years, only 21 cases of symptomatic CNS involvement have been diagnosed [10]. Although it is rare that patients receive a diagnosis of CNS involvement, most cases are asymptomatic. Therefore, after a diagnosis of CLL had been made, it is useful to perform screening examination with MRI.

CSF study, cytological examination of the CSF, and radiologic studies, such as computerized tomography (CT) or MRI, may assist with the diagnosis. In cytological examination of the CSF, the rate of a positive cytological specimen on the first lumbar puncture has been reported to be as low as 50% [11]. The CSF is abnormal in most patients, although its findings are nonspecific. Abnormalities include high protein, low glucose, and high white blood cell levels [11]. In our case, CSF evaluation performed at admission showed the nonspecific abnormalities described above. The cytological examination demonstrated small atypical lymphocytes in our case. Although they possibly were malignant cells, there were too few lymphocytes to make a definitive diagnosis. Therefore, it is difficult to diagnose CNS invasion by CLL with only a CSF study and cytological examination. Radiological studies may assist with the diagnosis. According to a study by Sato, MRI has more diagnostic value than CT [12]. In particular, it is difficult to diagnose dural invasion with CT because of nearby cranial bone [13], and dural invasion can be detected with MRI.

It is uncertain how the CLL cells gain access to the intracranial space. One hypothesis is that access is gained through extension along perforating vessels from the cranial bone to the dura mater or arachnoid membrane [14]. Another hypothesis is that malignant cells may spread along perineural sheaths of the cranial nerves or spinal nerve roots and gain entry into the intracranial space [15].

The most common origin of cancer that invades or metastasizes to the dura mater is the breast, followed by the prostate, lung, and hematological malignancy. Headache and cranial neuropathy are the most common presenting symptoms and signs. The same holds true for dural invasion of CLL. Formation of a mass has been reported in72% of all cases of dural metastases, and diffuse dural metastases, as in our case, have been reported in 25% of cases [16].

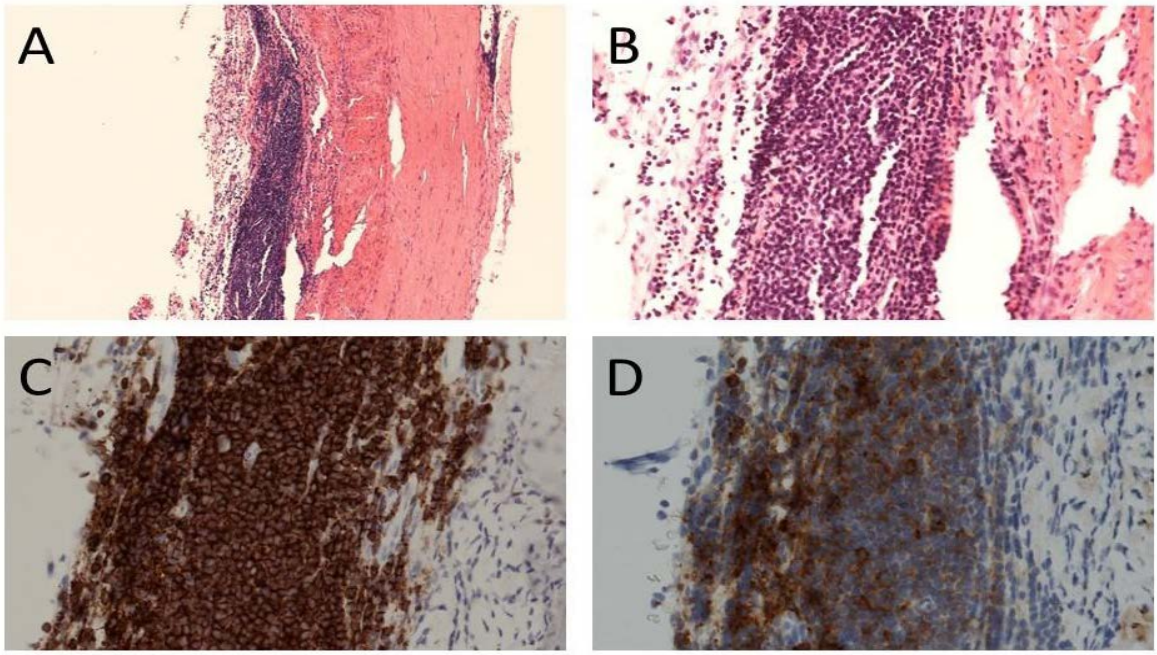


Figure 3: (A)(B) Histopathological examination showing many small lymphocytes in the medial dura (A: hematoxylin ans eosin(HE),× 200 B: HE, × 400).(C) Immunohiostochemical studies showing CD20+ and (D) CD23+

Radiation therapy has been the original method of treatment for CNS invasion by CLL. Total craniospinal axis radiation is no longer recommended because of the risk of myelosuppression, which is a possible side effect of chemotherapy for CLL. Irradiation is administered to areas of major clinical involvement [9]. Intrathecal chemotherapy also is useful and is delivered via lumbar puncture or through an intraventricular Ommaya reservoir. The latter method is recommended because this requires a surgical procedure for placement but eliminates repeated lumbar puncture on each administration [14]. Methotrexate is the most commonly used drug for intrathecal chemotherapy, and cytarabine or thiotepa also can be used. Along with the development of molecular target drugs, selection of the method of treatment requires reflection and experience.

## Conclusion

We described a case of dural invasion by CLL with characteristic radiological findings. Asymptomatic dural invasion by CLL is possible, and it is useful to perform a screening examination, such as MRI.

## Abbreviations

CLL: Chronic Lymphocytic Leukemia
MRI: Magnetic Resonance Imaging
CSF: Cerebrospinal Fluid
CNS: Central Nervous System
CT: Computed Tomography

## Competing Interests

The authors declare that they have no competing interests.

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