Case Report

Chronic Lymphocytic Leukemia With Central Nervous System Involvement: A High-Risk Disease?

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Clinical Practice Points

- Symptomatic direct involvement of the central nervous system (CNS) by chronic lymphocytic leukemia (CLL) is rare, with few cases occurring in patients with early-stage disease. Asymptomatic involvement of the CNS by CLL is much more prevalent.
- A heterogeneous clinical presentation and nonspecific imaging findings require a high level of suspicion. Diagnosis is usually confirmed by the presence of monoclonal lymphocytes with a CLL immunophenotype in the cerebrospinal fluid (CSF).
- There is no standard treatment for CLL with CNS involvement, although intrathecal chemotherapy with or without radiotherapy was used in most previously reported cases.
- We describe the case of a young patient with leptomeningeal and intraorbital CLL involvement who presented with diplopia as the initial symptom of CLL. She completely recovered with limited therapy that was based on risk assessment.
- This report demonstrates that patients who have CLL with CNS involvement can be successfully treated with standard chemoimmunotherapy.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, but neurologic complications arising from direct leukemic involvement of the nervous system are reported in only 1% of patients with CLL.[1,2] Here we describe a patient with untreated CLL who presented with leptomeningeal and intraorbital disease. The patient underwent standard chemotherapy and had a complete response to treatment with near-complete resolution of her neurologic symptoms. Although no standard protocol exists for CLL with central nervous system (CNS) involvement, the present case demonstrates that such presentation of CLL can be successfully treated with standard chemoimmunotherapy.

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Clinical Presentation

A 44-year-old white woman with a 1-month history of double vision was referred to M.D. Anderson Cancer Center. She had first noticed her vision impairment in the left lateral gaze and consulted her physician after her vision had gradually worsened. The patient had a 3-year history of asymptomatic Rai stage I CLL that had been diagnosed after routine mammography revealed axillary lymphadenopathy. In addition, a superficial melanoma was excised from her chest wall 1 year before her presentation at our institution.

On presentation to M.D. Anderson, the patient had an abduction deficit of the left eye, which raised the suspicion of an intraorbital process or lesion along the left cranial nerve VI. The patient also had a narrow left palpebral fissure and anisocoria. The patient denied having headache, fever, or other constitutional symptoms. No other signs of Horner syndrome were present, and iopidine test results were negative. The rest of the neurologic examination was unremarkable.

In addition, 1 × 1 cm lymphadenopathies were palpated in both cervical regions, and the spleen was palpated 2 cm below the left costal margin. Her laboratory workup was significant for a white blood cell count of 108,000/μL, and a peripheral blood smear revealed 91% lymphocytes and 2% neutrophils. Her hemoglobin level

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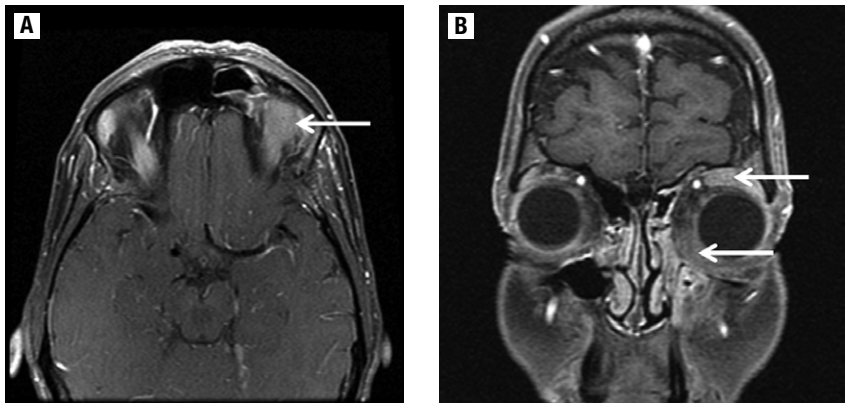
Figure 1 (A and B) Magnetic Resonance Images Showing Abnormal Soft Tissue in the Inferomedial and Superior Aspects of the Left Orbit (arrows)



was 11.7 g/dL and her platelet count was 148,000/μL. Her lactate dehydrogenase level was 845 IU/L (normal range, 313-618 IU/L), and her alkaline phosphatase level was 154 IU/L (normal range, 38-126 mg/dL). Her β_2-microglobulin level was 3.3 mg/L. Peripheral blood flow cytometry analysis was diagnostic of CLL. CD38 cell surface antigen was not detected. Fluorescence in situ hybridization detected trisomy 12 and 13q-, and conventional cytogenetic analysis of the peripheral blood revealed 9 abnormal metaphases with a hyperdiploid clone, 48XX, +12, +19, and 5 metaphases with a diploid female karyotype.

Further evaluation with magnetic resonance imaging (MRI) of the patient's head and neck revealed a diffuse abnormal hypointense T1 signal in the central base of the skull and left pterygopalatine fossa as well as a focus of abnormal soft tissue in the inferomedial aspect of the left orbit measuring 1.4 cm in greatest diameter (Figure 1A and B). These findings were suggestive of neoplastic infiltration of the central skull base and multifocal disease in the orbit. A diagnostic lumbar puncture was performed to obtain a cerebrospinal fluid (CSF) specimen. The CSF was clear and had normal glucose and protein levels and a red blood cell count of only 2/μL but a white blood cell count of 33/μL (normal range, 0-5/μL). Flow cytometry of the CSF revealed that the lymphocytes expressed both CD5 and CD19 cell surface antibodies, cell surface CD20(dim) and sIgλ but not CD10, confirming that CLL cells were present in the CSF but had not undergone lymphomatous transformation.

The patient was reluctant to undergo a diagnostic biopsy; therefore weekly treatments with 500 mg of methylprednisolone and 1000 mg of rituximab were started. After 4 weeks, the patient's vision had not improved significantly. MRI revealed regression of the masses in the inferior, medial, and superior aspects of the left orbit. Although the previously detected skull base and pterygopalatine fossa abnormalities remained unchanged, leptomeningeal disease was no longer present. Conventional detection methods and flow cytometry of CSF obtained with repeated lumbar punctures did not reveal CLL cells. Nevertheless, the patient was treated with intrathecal hydrocortisone (100 mg) and cytarabine (100 mg).

A transnasal endoscopic antrostomy, sphenoidotomy, and a biopsy of the skull at the pterygomaxillary space were performed. The biopsy specimens revealed infiltration of small aggregates of monoclonal lymphocytes with surface expression of CD5, CD19, CD20(dim), CD22, CD23, CD38, CD200, and sIgλ(dim) but not CD10 or FMC7 (Figure 2A and B), which was compatible with a diagnosis of CLL/small lymphocytic leukemia (SLL) with no evidence of transformation. The patient received treatment with intravenous fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2 every day from days 1 to 3, and 375 mg/m^2 rituximab on day 1 of cycle 1 and then 500 mg/m^2 from cycle 2 onward and was reevaluated after 3 courses. The patient's symptoms improved dramatically, and the cranial nerve VI paresis nearly resolved. Repeated MRI of the head and neck revealed significant disease regression, restoration of a relatively normal appearance of the bone marrow, and postoperative changes without signs of disease at the pterygopalatine fossa. The patient's peripheral blood counts, CSF specimens, and bone marrow aspiration and biopsy results showed no evidence of CLL and she has been followed for the past 5 months. Flow cytometry of bone marrow samples did not reveal minimal residual disease. The patient has not undergone additional therapy and remains under surveillance.

Discussion

Our patient presented with neurologic symptoms from intraorbital and leptomeningeal disease. Leptomeningeal disease as an initial presentation of untransformed CLL is exceedingly rare.[3] However a large autopsy study reported brain and leptomeningeal involvement in 20% and 8% of cases, respectively,[4] suggesting that CNS involvement in patients with CLL is underdiagnosed. Another study revealed that of 97 of autopsies in patients with CLL, 14 (14%) revealed orbital involvement.[5,6] A third study of 353 patients with lymphoma involving the structures of the eye