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

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Central nervous system; Chemoimmunotherapy; Chronic lymphocytic leukemia; Leptomeningeal dissemination; Neurologic involvement

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.

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

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Disclosure

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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 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 and surrounding tissue revealed SLL or CLL in only 13 patients (4%).[5,6]

None of the published studies revealed a correlation between leptomeningeal dissemination and the stage or duration of CLL.[7] Standard risk factors for CNS involvement in CLL have not been systematically explored. Patients with CLL with early-stage, long-standing, or advanced disease may experience localized leptomeningeal disease.[8,9] However a leptomeningeal dissemination of CLL cells in patients with early-stage disease is extremely rare. Among 67 reported patients with CLL who had CNS involvement, only 1 of 5 patients had CNS disease as a presenting symptom.[2]

The clinical manifestations of CLL involvement of the CNS are heterogeneous and include headache, cranial nerve palsies, cerebellar signs, visual problems, and motor and/or sensory deficits. Imaging studies are neither specific nor sensitive in the detection of CLL involvement of the CNS; the diagnosis is usually confirmed by lumbar puncture. In the present case, a traumatic lumbar puncture resulting in a CSF specimen contaminated with peripheral blood leukocytes was unlikely because only a few red blood cells and no myeloid cells were present in the sample. CLL cells can be recruited to sites of inflammation, and the presence of a monoclonal B-cell population in the CSF can be caused by inflammatory B-cell expansion.[10] The patient underwent excision of a melanoma 1 year earlier; however leptomeningeal melanoma would have a more aggressive clinical course, with MRI findings and immunohistochemical staining characteristic of the disease.[11] Therefore a diagnostic biopsy was performed.

The optimal treatment of patients who have CLL with CNS involvement is unclear. Most such patients undergo treatment that includes intrathecal chemotherapy with or without radiation therapy or systemic chemotherapy.[2] The most common intrathecal chemotherapy drugs include methotrexate, cytarabine, and corticosteroids used alone or in combination. Intrathecal chemotherapy with single-agent methotrexate has been shown to clear the CSF of CLL lymphocytes and resolve symptoms.[12] Calvo-Villas et al reported that sustained-release liposomal cytarabine cleared lymphocytes and resolved symptoms in 7 patients with CLL and Richter transformation with leptomeningeal involvement.[13] In most patients, only 1 dose was required to clear the leukemia cells from the CSF. Anecdotal cases showed efficacy with intrathecal thiotepa and with temazolamide.[14,15] Intrathecal rituximab is found to be effective in aggressive B-cell lymphomas, but no studies have reported its efficacy in CLL.[16]

The principal systemic drugs that penetrate the blood-brain barrier include high-dose methotrexate, cytarabine, and corticosteroids. For indolent leptomeningeal disease, fludarabine-based therapy has been found to be effective and may be a favorable therapeutic option because it is part of the standard CLL treatment.[17] Remarkably, dasatinib, a bcr-abl and Src tyrosine kinase inhibitor that is known to cross the blood-brain barrier, induced a long-lasting complete remission in a patient with CLL whose disease recurred in the nervous system after the patient underwent second-line chemotherapy.[18]

Although our patient was at high risk because of disease localization, she did not have high-risk CLL. According to the hierarchical model of genetic subgroups, patients with trisomy 12, such as in this patient, usually have intermediate-risk disease. Their CLL cells express higher CD20 antigen and respond well to FCR (fludarabine, cyclophosphamide, ritixumab) chemotherapy. As predicted by her disease characteristics, the patient attained remission with no signs of neurologic disease.

Conclusion

In general, patients who have CLL with direct neurologic involvement have a poor prognosis. Our experience described here suggests that treatment based on systemic chemoimmunotherapy can be effective in standard-risk patents.

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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.

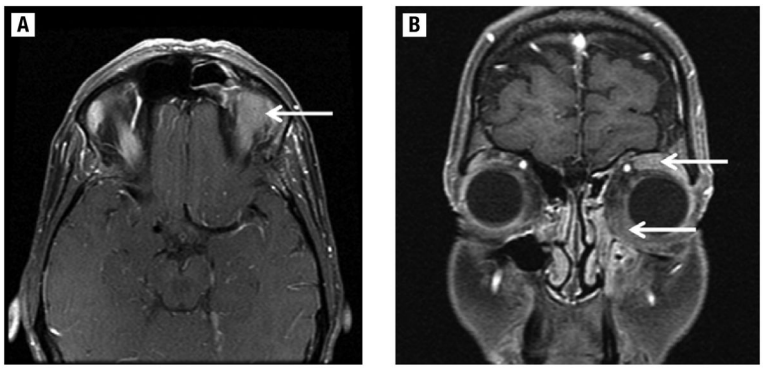

Figure 1.
(A and B) Magnetic Resonance Images Showing Abnormal Soft Tissue in the Inferomedial and Superior Aspects of the Left Orbit (arrows)

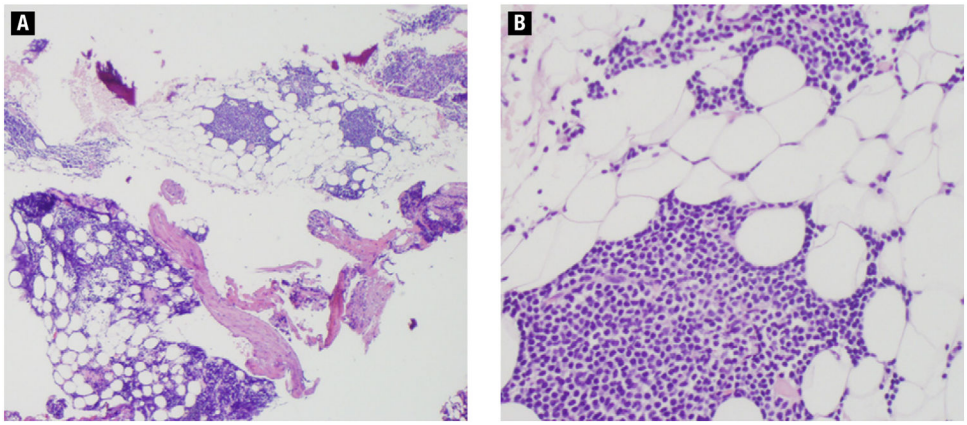

Figure 2.
(A and B) Left Pterygomaxillary Biopsy Specimens Showing Infiltration by Small Lymphocytes Forming Small Aggregates (Hematoxylin and eosin ×40 and ×200 original magnification.)