



CASE REPORT

Leukemic Meningitis in Chronic Lymphocytic Leukemia: A Rare Condition Responding to Intrathecal Methotrexate

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Introduction

Leukemic meningitis is a rare complication of chronic lymphocytic leukemia (CLL).¹⁻² The incidence of meningeal disease was 1% for patients with CLL in a retrospective Scandinavian study.³ The major components of treatment are intrathecal methotrexate and cranial irradiation.^{1,4,5} Complete resolution is attainable with no adverse neurologic sequelae.

Case Report

A 44-year-old male known to have CLL developed altered mental status six days after being admitted for neutropenic fever and herpes zoster. The patient's CLL was diagnosed four years prior to admission and initially treated with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy. His CLL was CD38 (+) which is indicative of a more aggressive course. He achieved remission, but relapsed three years later.

At that time, the patient was treated with fludarabine-cyclophosphamide to remission. The most recent relapse was about one year later. He was treated with pentostatin. The disease progressed 14 days after the administration of pentostatin. One month later, the patient was treated with salvage rituximab/hyper-CVAD (cyclophosphamide, vincristine, doxorubicine and dexamethasone) part B. Afterward, the patient was lost to follow up and missed the second cycle of chemotherapy. His whereabouts

were unknown for three months until he presented to the emergency room complaining of abdominal pain, nausea, vomiting, and severe fatigue.

The physical exam revealed a temperature of 103°F, ulceration of the posterior palate, supraclavicular adenopathy, splenomegaly palpated six centimeters below the costal margin, and an extensive vesicular dermatomal infiltrate extending from the midline of the back around the right flank to the midline of the abdomen. Similar lesions were noted over the trunk, right axilla, face, and scalp.

A complete blood count showed a white count of 13,500 (4% neutrophils); hemoglobin and hematocrit were 10.9 and 33.1 respectively. Sodium was 130, calcium was 11.9, and albumin 3.2 (corrected calcium = 12.86). The patient was admitted and started on IV vancomycin and cefepime for his neutropenic fever, IV acyclovir for his herpes zoster, IV fluids for his hypercalcemia (parathyroid hormone-related protein mediated response), and allopurinol to alleviate the effects of potential tumor lysis syndrome.

The patient had visual hallucinations (e.g., seeing animals) with confusion and agitation six days after admission. He had a history of alcoholism and was transferred to the intensive care unit, restrained, and treated with an alcohol withdrawal protocol. However, he showed no improvement. Interestingly, the patient told the nurses that

he was not having alcohol withdrawal as his previous experience with it was very different.

Given the presence of neutropenic fever, herpes zoster, and no improvement on the alcohol withdrawal protocol, a lumbar puncture was performed. It revealed glucose of 25, protein of 55, lactate dehydrogenase of 19, white count of 187 (95% of lymphocytes, 4% atypical lymphocytes) and the cerebrospinal (CSF) cytology revealed atypical lymphocytes.

The patient received hyper-CVAD cycle two. Intrathecal methotrexate 6mg was administered twice weekly. He had immediate resolution of the neurologic symptoms. Within 40 days, he manifested subsequent clearing of malignant cells in the cerebrospinal fluid and a Karnofsky score of 100 (i.e., no sign of disease).

Discussion

The differential diagnosis for the altered mental status in this case was broad. Alcohol withdrawal topped the list as the patient was an alcoholic having hallucinations after six days in the hospital. The lumbar puncture was necessary to reveal the leukemic meningitis.

The manner in which leukemic cells enter the central nervous system (CNS) is a

subject of controversy, but the likely sources include hematogenous spread or direct spread from adjacent infiltrated bone marrow. The most common form of CNS spread or meningeal form of leukemia are divided in four categories: increased intracranial pressure (with vomiting, headache, papilledema, lethargy, seizure, and/or coma), visual disturbances (with diplopia, blurred vision, blindness, and/or photophobia), CNS palsies (e.g., in cranial nerves VI or VII), and other (with myelopathy, auditory, vertigo, ataxia, hallucinations, and/or nystagmus).⁶

The major components of the treatment for leukemic meningitis in CLL are intrathecal methotrexate and cranial irradiation.^{1,4,5} Intrathecal steroids were used to treat the chemotherapy-induced encephalopathy.^{2,5,7} Rituximab was reported to be effective in a case refractory to the conventional chemotherapy.⁷ Fludarabine also was suggested to be helpful in inducing durable remission in patients with leptomeningeal involvement of CLL.⁸

The present case illustrated that a complete resolution of the leukemic meningitis associated with CLL is attainable with intrathecal methotrexate with no adverse neurologic sequelae.

References

- 1 Wang ML, Shih LY, Dunn P, Kuo MC. Meningeal involvement in B-cell chronic lymphocytic leukemia: Report of two cases. *J Formos Med Assoc* 2000; 99:775-778.
- 2 Brick WG, Majmundar M, Hendricks LK, Kallab AM, Burgess RE, Jillella AP. Leukemic leptomeningeal involvement in stage 0 and stage 1 chronic lymphocytic leukemia. *Leuk Lymphoma* 2002; 43:199-201.
- 3 Weizsaecker M, Koelmel HW. Meningeal involvement in leukemias and malignant lymphomas of adults: Incidence, course of disease, and treatment for prevention. *Acta Neurol Scand* 1979; 60:363-370.
- 4 Marmont A. Leukemic meningitis in B-cell chronic lymphocytic leukemia: Resolution following intrathecal methotrexate. *Blood* 2000; 96:776-777.
- 5 Watanabe N, Takahashi T, Sugimoto N, et al. Excellent response of chemotherapy-resistant B-cell-type chronic lymphocytic leukemia with meningeal involvement to rituximab. *Int J Clin Oncol* 2005; 10:357-361.

- ⁶ Ginsberg LE, Leeds NE. Central nervous system complications of leukemia. 2002. Accessed at: <http://www3.mdanderson.org/depts/rpi/di/cnsc11.html>.
- ⁷ Remková A, Bezayová T, Vyskocil M. B cell chronic lymphocytic leukemia with meningeal infiltration by T lymphocytes. *Eur J Intern Med* 2003; 14:49-52.

- ⁸ Knop S, Herrlinger U, Ernemann U, Kanz L, Hebart H. Fludarabine may induce durable remission in patients with leptomeningeal involvement of chronic lymphocytic leukemia. *Leuk Lymphoma* 2005; 46:1593-1598.

Keywords: chronic lymphocytic leukemia, meningitis, methotrexate