Meningeal Involvement in B-Cell Chronic Lymphocytic Leukemia: Report of Two Cases

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Abstract: Symptomatic central nervous system (CNS) involvement in chronic lymphocytic leukemia (CLL) or its variants is rare. We report two cases of CLL with leptomeningeal involvement. Patient one was an 81-year-old male who had CLL stage C (IV) at diagnosis and developed meningeal disease 29 months later. Patient 2 was a 42-year-old male with a diagnosis of CLL stage A (II) that evolved into mixed-cell CLL/prolymphocytic leukemia (PLL) 1.5 years later, with leptomeningeal infiltration of prolymphocytes developing 26 months after initial diagnosis. Meningeal leukemia was diagnosed by cerebrospinal fluid examination, with flow cytometry showing the same immunophenotypic findings of λ-light chain restriction as the lymphocytes in bone marrow in one patient, and with morphologic characteristics exhibiting exclusively prolymphocytes in the other patient. The CNS disease of both patients responded effectively to intrathecal chemotherapy and cranial irradiation. However, both patients died of infection, a major cause of morbidity and mortality in patients with CLL. The clinicopathologic features of these two patients indicate that, despite the rarity of CNS involvement in CLL patients, any neurologic manifestation in CLL patients should arouse suspicion of meningeal leukemia and patients should be examined and managed accordingly.

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intrathecal chemotherapy

Although meningeal leukemia frequently occurs during the course of acute leukemia and non-Hodgkin's lymphoma, its occurrence in chronic lymphocytic leukemia (CLL) or prolymphocytic leukemia (PLL) is rare [1, 2]. The meningeal illness may begin insidiously but progress rapidly. A definite diagnosis of leptomeningeal involvement in CLL or its variants is always delayed; because leptomeningeal involvement is rare in CLL and the initial manifestations are subtle, clinicians often fail to make an early diagnosis. Early diagnosis and appropriate therapy is mandatory to resolve neurologic dysfunction. Here, we describe two cases of CLL complicated by meningeal leukemia.

Case Reports

Case 1

CLL was diagnosed in this 81-year-old man in March 1992 when he visited the hospital after experiencing dizziness, general malaise, and exertional precordial discomfort. Physical examination revealed cervical lymphadenopathy and splenomegaly which was palpable 5 cm below the left costal margin. His hemoglobin concentration was 11.2 g/dL, platelet count was 79.0 x 10^9/L, and leukocyte count was 62.6 x 10^9/L with 94.8% small mature lymphocytes. Bone marrow aspirate smear showed 79% mature lymphocytes. Liver and

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renal function tests were within normal limits. The concentration of serum albumin was 4.5 g/dL, globulin 1.5 g/dL with an IgG of 794 mg/dL, lactate dehydrogenase (LDH) 89 U/L (normal 47–140 U/L), and β_2-microglobulin 618 μg/L (normal 800–2,400 μg/L). Immunophenotypic analysis of bone marrow lymphocytes by flow cytometry showed that the lymphocytes expressed CD5 (53%), CD20 (83%), CD23 (59%), HLA-DR (86%), λ-light chain (81%), and surface immunoglobin (sIg) 78% (dim), but did not express κ-light chain (< 1%) or other T-cell markers including CD2, CD3, CD4, and CD8. A diagnosis of CD5+ B-CLL stage C (IV) was made [3, 4]. The patient received chlorambucil intermittently in the following 2 years.

In August 1994, he suffered from insomnia and a slow onset of headache over the parieto-occipital area that progressively increased in severity over a 1-month period. There was no fever or motor deficit. Neurologic examination revealed slight confusion, but no neck stiffness, cranial nerve palsy, or motor weakness. The complete blood count showed a hemoglobin concentration of 11.7 g/dL, red blood cell (RBC) count of 4.37 x 10^{12}/L, white blood cell (WBC) count of 23.9 x 10^9/L with 72% small lymphocytes, and a platelet count of 185 x 10^9/L. Brain computed tomography (CT) scan showed no abnormalities. Lumbar puncture yielded clear and colorless cerebrospinal fluid (CSF), and the opening pressure was normal. The CSF leukocyte count was 87 x 10^6/L with 100% small mature lymphocytes, and the RBC count was 3 x 10^6/L. Immunophenotypes of CSF cells were identical to those of bone marrow lymphocytes, expressing CD20, CD5, and λ-light chain. Cultures for bacteria and acid-fast bacillus were all negative. Leukemic leptomeningeal involvement was diagnosed. The patient then received intrathecal methotrexate (15 mg) twice per week followed by whole-brain irradiation. Although the headache improved dramatically, he died of *Enterobacter cloacae* sepsis 3 weeks after the diagnosis of meningeal involvement.

Case 2

A 42-year-old male presented with general malaise and abdominal fullness of 1-year duration in December 1992. Physical examination revealed an enlarged spleen palpable at the umbilical level but no peripheral lymphadenopathy. The blood counts were: hemoglobin 14.2 g/dL, WBC count 57.6 x 10^9/L with 84% small mature lymphocytes, and platelet count 174.0 x 10^9/L. The bone marrow aspirate smear showed 76% small mature lymphocytes. The LDH concentration was 56 U/L and β_2-microglobulin concentration was 3,043 μg/L. The immunophenotypes of bone marrow lymphocytes were CD5 (94%), CD20 (92%), CD2 (9%), CD3 (7%), CD4 (4%), CD8 (4%), κ-light chain (91%), and λ-light chain (< 1%). A diagnosis of CD5+ B-CLL A (II) was made. To relieve the symptomatic splenomegaly, the patient was treated with chlorambucil and prednisolone from September 1993 to April 1994. In April 1994, the blood counts showed a hemoglobin concentration of 12.1 g/dL, a platelet count of 140.0 x 10^9/L, and leukocyte count of 37.3 x 10^9/L with 27.8% prolymphocytes. The immunophenotypes of peripheral blood lymphocytes were CD5 (58%), CD20 (90%), CD2 (5%), CD3 (4%), CD4 (1%), CD8 (2%), sIg (76%) (dim), HLA-DR (87%), κ-light chain (90%), and λ-light chain (< 1%). The hematologic features and immunophenotypic findings were consistent with CLL/PLL as defined by the FAB Cooperative Group [5]. One cycle of cyclophosphamide, vincristine, and prednisolone (COP) was initiated in October 1994, followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) because of progressive hepatosplenomegaly with rapid development of massive pleural effusion. The pleural effusion completely resolved following combination chemotherapy with CHOP, but hepatosplenomegaly remained unchanged.

On February 9, 1995, severe headache, vomiting, and blurred vision developed, which was followed by seizure and loss of consciousness 3 days later. Physical examination revealed neck stiffness and limited lateral gaze of the left eye. Brain CT scan revealed mild dilatation of the temporal horns and rounding of the anterior recess of the third ventricle, which suggested minimal communicating hydrocephalus. Lumbar puncture was performed and disclosed an opening pressure of 600 mm H_20 and a terminal pressure of 420 mm H_2O with an elevated protein concentration (82 mg/dL), decreased glucose concentration (21 mg/dL), and lymphocytosis (2.088 x 10^9/L) in the CSF. The CSF lymphocytes were exclusively prolymphocytes with clumped chromatin and prominent nucleoli (Figure). Acid-fast stained smear and cultures for bacteria, fungi, and mycobacterium were negative. The blood counts showed a hemoglobin concentration of 10.3 g/dL, a WBC count of 2.1 x 10^9/L with segments 17%, monocytes 14%, small lymphocytes 59% and prolymphocytes 10%, and a platelet count of 70 x 10^9/L. The LDH concentration was 115 U/L and β_2-microglobulin was 2,143 μg/L. The patient was treated with intrathecal methotrexate injections and cranial irradiation. Neurologic function returned to normal within 2 weeks. The CSF abnormalities were completely resolved after six doses of intrathecal chemotherapy and 2350 cGy whole brain irradiation. He remained neurologically asymptomatic until 3 months later, when severe neutropenia (leukocyte count 0.1 x 10^9/L) developed after another cycle of CHOP, and he died of sepsis with no clinical evidence of meningeal disease.

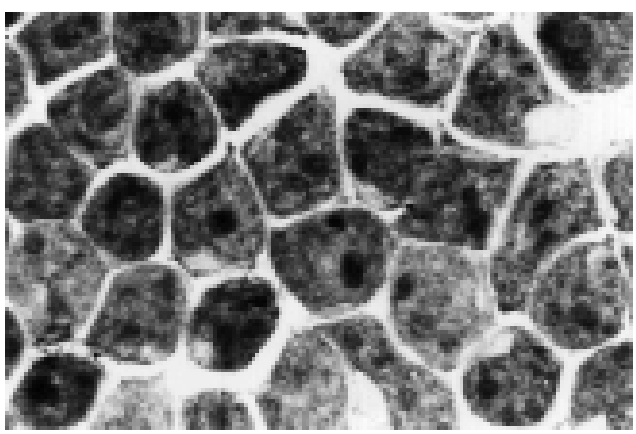

Figure. *Cytospin preparation of cerebrospinal fluid cells showing prolymphocytes with a distinct nucleolus and a moderate degree of chromatin condensation (Liu stain, 1,000 x).*

Discussion

Although CLL is the most common leukemia in Western countries, it is relatively rare among Orientals. Extramedullary tissue infiltration, particularly of the spleen, liver, and lymph nodes, is frequently observed in advanced-stage CLL. Barcos et al reviewed the autopsy findings of 109 patients with CLL and found leptomeningeal infiltration in 8% [2]; however, symptomatic CNS involvement has rarely been reported in CLL. Our review of the literature identified 15 well-documented cases of B-CLL or its variants with symptomatic CNS disease [6–17], two of which had parenchymal brain tumor without leptomeningeal involvement [6, 7]. Of the remaining 13 cases, seven had stage III or IV disease, four had stage 0 disease, and the stage of the remaining two was not specified [3, 4]. Meningeal involvement in CLL occurred at various time points during the disease course, ranging from the time of initial presentation to 14 years after diagnosis when systemic disease had progressed. Thus, the risk of symptomatic meningeal involvement was not related to stage or duration of CLL. One of our two patients developed CNS disease 29 months after diagnosis of stage IV disease, and the other at the time of transformation to CLL/PLL, 26 months after the diagnosis of CLL stage A (II).

CNS involvement in leukemia/lymphoma frequently presents a diagnostic challenge. The neurologic manifestations of CNS involvement in the reported cases varied from fever, headache, lethargy, decreased cognitive function, sensory abnormality, motor weakness, and cranial nerve palsy to coma, and could mimic infectious, thrombotic, or hemorrhagic complications. The role of CSF examination in differentiating these conditions is well documented. Nevertheless, difficulties exist in using morphologic criteria to distinguish between neoplastic small lymphocytes and benign reactive lymphocytes present in CSF, because lymphocytes in both disorders are morphologically almost identical. As a result, in addition to routine cytologic studies, the immunophenotypic analysis of lymphoid cells in the CSF is very important in the diagnosis of the clonal nature of cells in the CSF. The immunophenotyping of CSF cells from patient 1 confirmed leptomeningeal infiltration with clonal lymphocytes that were identical to leukemic cells from bone marrow and blood and expressed light-chain restriction of the same type. Although immunophenotypic analysis of neoplastic cells in the CSF was not performed in patient 2, cytologic examination demonstrated the characteristic morphologic features of prolymphocytes exhibiting a distinct nucleolus and a moderate degree of chromatin condensation. Only five cases of leptomeningeal involvement by prolymphocytes in PLL or CLL/PLL have been reported. Among them, two had a classic initial presentation of PLL [14, 16] and the other three developed prolymphocytic meningeal leukemia against a background of CLL/PLL in bone marrow and peripheral blood, as in our patient 2 [6, 15, 17]. Since CLL occurs most often in the elderly population, its presentation as a cognitive problem can easily be misinterpreted as lethargy or dementia. It should be stressed that the possibility of CNS leukemia should be taken into consideration in CLL patients presenting with neurologic symptoms.

The therapy for CNS disease in CLL or CLL/PLL varied widely in the reported cases, and included systemic intravenous chemotherapy, intrathecal chemotherapy alone, or intrathecal chemotherapy plus cranial irradiation. A wide range of responses to treatment of meningeal leukemia have been reported [6, 7, 15]. Nevertheless, as in the two patients of this report, most patients had improvement in symptoms when treated with intrathecal chemotherapy and/or cranial irradiation. There were only three deaths due to uncontrolled CNS disease, all of which were diagnosed too late to be treated [6, 11, 18]. Data from previous reports as well as the present two cases suggests that an accurate diagnosis followed by pertinent treatment will lead to complete resolution of neurologic manifestations as well as a rapid clearing of leukemic cells from the CSF [6, 7].

Despite advances in therapeutic approaches to CLL, infection remains the major cause of morbidity and mortality in patients with CLL [19]. Both of our patients died of infection rather than of uncontrolled meningeal disease. Patients with CLL are predisposed to infections due to the primary disease process as well as due to further immunosuppression induced by therapy with cytotoxic agents and corticosteroids.

In summary, although CLL with leptomeningeal involvement is uncommon, meningeal involvement in CLL may occur during the course of the disease, and usually responds to intrathecal chemotherapy and cranial irradiation. The data from reported cases as well as our two patients indicate that meningeal involvement should be included in the differential diagnosis when patients with CLL develop any neurologic abnormality, and cytologic examination plus immunophenotypic analysis of the CSF should be performed to establish the diagnosis and appropriate therapy.

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