Acta Scientific Cancer Biology

Volume 1 Issue 1 June 2017

Case Report

CLL with CNS Involvement - A Diagnostic Dilemma

Rakul Nambiar K[1], Anoop TM[2]* and Prakash NP[3]

[1]*Senior Resident, Department of Medical Oncology, Regional Cancer Centre, India*

[2]*Assistant Professor, Department of Medical Oncology, Regional Cancer Centre, India*

[3]*Additional Professor, Department of Medical Oncology, Regional Cancer Centre, India*

***Corresponding Author:** Anoop TM, Assistant Professor, Department of Medical Oncology, Regional Cancer Centre, Trivandrum, India.

Received: June 13, 2017; **Published:** July 31, 2017

Abstract

Chronic lymphocytic leukemia (CLL), a clonal disorder of B lymphocytes is the most common lymphoproliferative disorder in the Western world. Extramedullary neoplastic infiltration of CLL has been described in skin, lung, pleura, gastrointestinal tract and kidney. However, involvement of the central nervous system (CNS) is considered to be rare and symptomatic central nervous system involvement in CLL is known to be rarer. Further, reported cases of CNS involvement of CLL demonstrated a diverse and non-specific spectrum of symptoms including headaches, mental status changes, cerebellar signs, cranial nerve abnormalities and weakness of extremities. This varied presentation of symptomatic central nervous system involvement in CLL leads to diagnostic difficulties. Here we report an unusual case of a 40-year-old female with untreated CLL who was diagnosed to have CNS involvement and was treated with intrathecal and systemic chemotherapy. The diagnostic dilemma arose when she presented 8 months later with similar symptoms. We are reporting the case to highlight the fact that neurological symptoms in a CLL patient may not always be due to the disease and other etiologies must also be considered in the differentials.

Keywords: CLL; CNS Involvement

Introduction

Chronic lymphocytic leukemia (CLL), a clonal disorder of B lymphocytes is the most common lymphoproliferative disorder in the Western world [1]. CNS involvement in CLL is rare and only less than 100 cases of CNS involvement by CLL have been described in literature. However, autopsy findings in CLL patients illustrate the fact that CLL cells may be frequently present in the CNS but rarely cause clinically significant manifestations. This makes the evaluation of neurological symptoms in CLL patients challenging. The mere presence of CLL cells in CSF does not definitely indicate that CLL is the etiology of the patients' neurological symptoms. Moreover, the varied neurological conditions that occur in patients with CLL include infections, other malignancies, autoimmune/ inflammatory diseases, and non-CLL-related medical conditions. We present the diagnostic dilemma we faced in a CLL case with established CNS disease when she presented with recurrent symptoms.

Case Report

A 40-year-old lady presented with a 2-week history of headache. Her headache was initially waxing and waning in intensity which later became persistent and progressive. The patient was recently diagnosed (1month ago) with asymptomatic Rai stage I CLL. On examination, her Eastern Cooperative Oncology Group performance score was 2 and her physical examination was within normal limits. Her laboratory workup was significant for a white blood cell count of 144,000/μL, and a peripheral blood smear revealed 44% atypical lymphocytes. Her hemoglobin level and platelet count were 10.4 g/dL and 682,000/μL respectively. Her lactate dehydrogenase level was 728 IU/L (normal range, 313-618 IU/L) and her MRI brain was normal. CSF study showed elevated protein (157 mg/dl), normal glucose (70 mg/dl) with elevated cells (540 cells/ cumm) which were predominantly lymphocytes (99%) and hence, a provisional diagnosis was chronic meningitis was made.

However, immunobiotic chemical staining showed that the lymphoid cells were CD 5 and CD 23 positive which was consistent with a diagnosis of chronic lymphocytic leukemia infiltration. She was started on fludarabine, cyclophosphamide, rituximab (FCR regimen) and intrathecal chemotherapy with methotrexate, cytarabine and hydrocortisone. She received 6 cycles of chemotherapy with intrathecal chemotherapy. She attained remission and was kept under follow-up. However, a month later she presented with herpes zoster infection for which she was treated with acyclovir. She again presented a week later with severe headache and vomiting.

Considering the possibility of CNS relapse, a CSF study was done which showed similar findings (elevated protein, normal glucose and lymphocytosis). Though there was lymphocytosis the pic-

ture was more in favor of aseptic meningitis. In view of the recent herpes zoster infection and her immunocompromised state (due to CLL) the possibility of viral aseptic meningitis was considered and she was treated with parenteral acyclovir. She improved symptomatically and her repeat CSF post treatment was within normal limits. At present, she is off medications and is doing well at 1 year follow-up.

Discussion

CNS involvement of CLL is a poorly studied phenomenon in literature. The clinical manifestations of CLL involvement of the CNS are heterogeneous which include headache, cerebellar signs, cranial nerve palsies, visual problems, and motor or sensory deficits. There appears to be no correlation between CNS involvement and disease stage in CLL, duration of CLL, gender, age, peripheral leukocyte count or immunologic phenotype and interestingly most cases of CNS involvement by CLL occurred in early stage and previously untreated patients [2,3]. The time from CLL diagnosis to CNS documentation of disease varied from 0 days to 15 years (median - 4.5 years) [2].

Imaging studies are neither specific nor sensitive in the detection of CLL involvement of the CNS [4,5]. The cornerstone for the diagnosis of CLL leukemic infiltration of the CNS is proving the monoclonality of the cytologically abnormal malignant lymphocytes in the CSF; however, interpretation of CSF analysis can be particularly difficult. Hence, flow cytometry is often needed to distinguish between reactive lymphocytes and CLL B cells [6,7] and the presence of CLL B cells in the CSF does not necessarily indicate CLL as the etiology of the patient's neurological disease. CLL cells tend to traffic to sites of inflammation and can often be present as an innocent bystander in patients with infections or other inflammatory conditions [8]. Contamination of the CSF by peripheral blood (due to bloody tap) can also result in detection of CLL B cells in the CSF. Hence a complete comprehensive work up is necessary to exclude other etiologies of neurological symptoms rather than assuming the mere presence of CLL B cells in the CSF as an indication that CLL is the etiology of the patient's neurological symptoms. The specificity of the presence of CLL B cells in the CSF study is relatively poor.

The interpretation of CSF analysis may be further complicated by CNS infections. First, due to derangements of humoral and cellular immune functions, CNS opportunistic infections may be associated with false positive CSF cytologies. Viral meningitis is classically described as being associated with a lymphocytic CSF, but polymorphonuclears may predominate, especially early during the course of the illness.

At present, there are no established guidelines for treatment of CLL patients with CNS involvement. Most patients have been treated with intrathecal chemotherapy with or without radiation therapy or systemic chemotherapy. Intrathecal rituximab has been found to be effective in aggressive B-cell lymphomas, however its efficacy in CLL has not been reported [9]. For CLL patients with indolent leptomeningeal disease, fludarabine-based therapy has been found to be effective and may be a favorable therapeutic option [10].

Conclusion

In conclusion, neurological symptoms occur relatively frequently in patients with CLL; however clinically significant CNS involvement by CLL is rare. The presence of CLL B cells in the CSF has reasonable sensitivity but relatively low specificity and is insufficient to establish CLL as the etiology of patients' neurological symptoms. A complete neurological evaluation including imaging, CSF analysis, and evaluation for a wide range of other conditions (infectious and inflammatory) is needed to determine the etiology of neurological symptoms in these patients.

Bibliography

1. Chiorazzi N., *et al.* "Chronic lymphocytic leukemia". *The New England Journal of Medicine* 352.8 (2005): 804-815.

2. Lopes da Silva R. "Spectrum of neurologic complications in chronic lymphocytic leukemia". Clin Lymphoma Myeloma Leuk 12.3 (2012): 164-179

3. Cramer SC., *et al.* "Chronic lymphocytic leukemia and the central nervous system: a clinical and pathological study". *Neurology* 46.1 (1996): 19-25.

4. Watanabe N., *et al.* "Excellent response of chemotherapy-resistant B-cell-type chronic lymphocytic leukemia with meningeal involvement to rituximab". *International Journal of Clinical Oncology* 10.5 (2005): 357-361.

5. Hanse MC., *et al.* "Incidence of central nervous system involvement in chronic lymphocytic leukemia and outcome to treatment". *Journal of Neurology* 255.6 (2008): 828-830.

6. Amiel JL and Droz JP. "Letter: spinal lymphocytosis dur-

ing chronic lymphocytic leukemia". *La Nouvelle Presse Medicale* 5.2 (1976): 94-95.

7. Singh AK and Thompson RP. "Leukaemic meningitis in chronic lymphocytic leukaemia". *Acta Haematologica* 75.2 (1986): 113-115.

8. Nowakowski GS., *et al.* "Clinical significance of monoclonal B cells in cerebrospinal fluid". *Cytometry Part B: Clinical Cytometry* 63.1 (2005): 23-27.

9. Rubenstein JL., *et al.* "Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma". *Journal of Clinical Oncology* 25.11 (2007): 1350-1356.

10. Knop S., *et al.* "Fludarabine may induce durable remission in patients with leptomeningeal involvement of chronic lymphocytic leukemia". *Leukemia and Lymphoma* 46.11 (2005): 1593-1598.

Volume 1 Issue 1 June 2017