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Chronic Lymphocytic Leukemia With Meningeal Infiltration By Monoclonal T Lymphocytes

Monoklonal T Lenfositlerce Meningeal İnfiltrasyonun Olduğu Bir Kronik Lenfositik Lösemi Vakası

Hematoloji

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Anıl Tombak[1], Feray Tabakan[1], Gülçin Eskandari[1], Eyüp Naci Tiftik[1]

[1] Mersin Üniversitesi Tıp Fakültesi Hastanesi

Özet

Kronik lenfositik lösemi (KLL) monoklonal B lenfositlerin proliferasyonu ve birikimi ile karakterizedir. Leptomeningeal tutulum, nadir bir komplikasyonudur ve sıklıkla T-hücreli lösemilerde görülür. Burada, baskın olarak monoklonal T lenfositlerce leptomeningeal infiltrasyonun olduğu 70 yaşındaki KLL'li bir erkek hastayı sunmaktayız. Nörolojik bulgular,hastalığın ilk belirtileri oldu. Beynin manyetik rezonans görüntülemesi normaldi. T-hücreli lösemik menenjit tanısı, serebrospinal sıvının sitolojik ve akım sitometrik incelemesi ile konuldu. Hasta hem sistemik, hem de intratekal kemoterapi ile tedavi edildi. Bununla beraber, nötropenik ateş nedeniyle öldü. Bu nadir KLL vakasının, periferal B hücreler, fakat meningeal T hücrelerle birlikte biklonal olduğunu düşünmekteyiz.

Anahtar kelimeler: *Kronik lenfositik lösemi, Leptomeningeal tutulum Biklonal*

Abstract

Chronic lymphocytic leukemia (CLL) is characterized by the proliferation and accumulation of monoclonal B lymphocytes. Leptomeningeal involvement is a rare complication and usually seen in T-cell leukemias. Here, we report a 70-year-old man with CLL and leptomeningeal infiltration by predominantly monoclonal T lymphocytes. Neurological symptoms were the first manifestations of the disease. Magnetic resonance imaging of the brain was normal. The diagnosis of T-cell leukemic meningitis was made by cytological and flow cytometry analysis of cerebrospinal fluid. The patient treated with both systemic and intrathecal chemotherapy. However, he died because of neutropenic fever. We think that this rare case of CLL was biclonal with peripheral B-cells, but meningeal T-cells.

Keywords: *Chronic lymphocytic leukemia, Leptomeningeal involvement Biclonal*

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the proliferation and accumulation of monoclonal B lymphocytes. Usually, CLL progresses slowly and as the disease progresses; malign cells infiltrate the bone marrow, lymph nodes, spleen and liver.[1] Involvement of the central nervous system is a rare complication of CLL.[2] It is usually seen in T-cell leukemias.[3] In cases of T-cell prolymphocytic leukemia, (T-PLL), epidermal sites and the central nervous system are more likely to become involved.[4] We report a case of CLL with meningeal infiltration by both B and T lymphocytes, but predominantly by monoclonal T lymphocytes.

Case Report

A 70-year-old man who was diagnosed as stage I CLL on November-2008 admitted to our hospital on April, 2011 with a history of headache and reduction in hearing for 1 month. He was under control without any treatment and had no co-morbid conditions except CLL. Physical examination on admission revealed 3 cm splenomegaly under cot margin, and stiff neck. No enlargement of peripheral lymph nodes was observed. His body temperature was 38 ºC. Fundoscopy revealed age related macular degeneration. Computed tomography (CT) and magnetic

Sorumlu Yazar: Anıl Tombak, Mersin Üniversitesi Tıp Fakültesi Hastanesi
Mersin Üniversitesi Tıp Fakültesi Hastanesi İç Hastalıkları-Hematoloji BD.
aniltombak@mersin.edu.tr

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resonance imaging (MRI) of the brain were within normal limits. The patient was hospitalized with a pre-diagnosis of meningitis; a cerebrospinal fluid (CSF) puncture was carried out and ceftriaxon was started empirically. A high protein concentration (total protein: 5386 mg/L) and pleocytosis (8200 /mm^3 and almost all cells were mature lymphocytes) were revealed by analysis of the CSF (Figure 1).

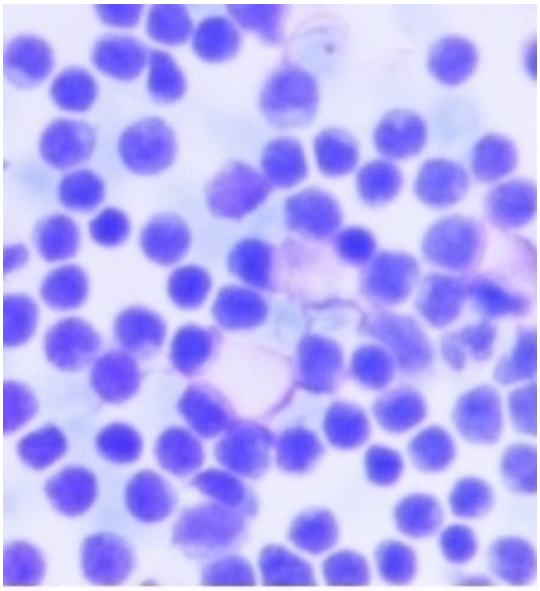

Figure 1
Mature lymphocyte infiltration of cerebrospinal fluid (Giemsa staining).

Microscopic examination, using a Gram stain of smears failed to reveal any pathogens in CSF. Laboratory tests showed leukocytosis (white blood cells: 57000 /mm^3 with lymphocytes: 46000 /mm^3), anemia (8.3 g/dl), and normal thrombocyte count (177000 /mm^3). In the blood smear, 80% of all white blood cells were mature lymphocytes and basket cells were also observed. On biochemical examination, normal values of serum bilirubin, urea, uric acid, albumin, globulin, transaminases, alkaline phophatase, sodium, potassium, calcium, cardiac enzymes, and blood glucose were found. The erythrocyte sedimentation rate was 39 mm/h, the values of serum C-reactive protein (CRP), plasma fibrinogen and procalcitonin were within normal limits. His chest X-ray was normal. Abdominal ultrasonography disclosed splenomegaly (185 mm) and multiple lympadenopathies of which the largest one is 3 cm in diameter.

The CSF cultures, and also the initial blood cultures were all negative. Using the serological tests, we failed to find a rise in antibody titers against *Toxoplasma, Mycoplasma pneumonia,* cytomegalovirus, herpes simplex virus, and Epstein-Barr virus. Cultures of CSF for tuberculosis (Löwenstein-Jensen) were also negative. Immunophenotyping of the peripheral blood and CSF cells with monoclonal antibodies by flow cytometry were performed simultaneously. In the lymphocytic population determined in peripheral blood (87% of all leukocytes), there was the presence of a cell clone with the following codes: CD5 (92%), CD19 (92%), CD20 (92%), CD22 (92%), CD23 (86%), CD38 (89%). Chronic lymphocytic leukemia diagnosis was documented by the co-expression of CD19/23 and CD5/20. Additionally, there was a depletion of T-cell codes; 6% of the lymphocytes were positive for CD3 and 98% of these CD3 cells were positive for TCRα/ß and ɣ/&.

Interestingly, flow cytometry of CSF showed that 80% of these lymphocytes were CD3, 16% were CD19 positive. Ninety five percent of these CSF lymphocytes expressed CD5; 19% of these CD5 positive lymphocytes co-expressed CD5/CD19 (CLL cells) and 76% of these were not positive for CD19 [CD5(+)/CD19(-) : malign T-cell clone]. Also, 15% co-expressed CD19/CD23 (CLL cells) while 65% co-expressed CD3/CD7 and 21% of these CD3 cells were CD8 positive, 68% were CD38 positive. CD3/TCR α/ß co-expression was 77%, while

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TCRɣ/& was not expressed in CD3 lymphocytes. Fifty eight percent of all lymphocytes were CD38 positive and CD19/38 co-expression was 23%. Consequently, a dominant T-cell clone (80%) and a few B-cell clones (16%) were determined in CSF (Table 1).

T-cell clone (80%)	CD3 (+)	CD5(+)/CD19(-)	CD3/CD7 (+)	CD3/CD4 (+)	CD3/TCRα/ß (+)	CD3(+)/TCRɣ/&(-)	CD38 (+)
B-cell clone (16%)	CD19 (+)	CD5/19 (+)	CD19/23 (+)	CD20 (+)	CD22 (+)	CD23 (+)	CD38 (+)

Table 1
Flow cytometric analysis of the lymphocytes in the central nervous system.

Cytology of CSF was reported as “infiltration of CSF by lymphocytic cells”. Intrathecal chemotherapy (by repeated lumbar puncture) with methotrexate (12 mg), cytarabine (70 mg) and dexamethasone (4 mg) was administered for lymphoid meningeal infiltration. Simultaneously, CHOP (cyclophosphamide, daunorubicin, vincristine, prednisolone) chemotherapy regimen was started systematically. After 1 week of intrathecal therapy, a new CSF puncture was carried out and it was found that the leukocyte count was decreased to 4000/mm3 from 8200 /mm^3 and again all cells were mature lymphocytes. However, the patient died because of neutropenic fever (*klebsiella* sepsis) after 3 weeks of hospitalization.

Discussion

CLL is lymphoproliferative disorder of mature small B-cells characterized with co-expression of B-cell markers (CD19, CD20, CD22, and CD79a) with CD23, and CD43. There is also co-expression of CD5 (pan T-cell antigen), but not the other T-cell antigens.[1] B and T lymphocytes cannot be distinguished morphologically. Because of the indolent nature of CLL, organ involvement other than the bone marrow, spleen, and lymph nodes is exceptional.[2] Leptomeningeal involvement in patients with CLL is relatively rare (1-2%) and the prognosis is usually poor.[3] There is a higher incidence of central nervous system involvement in T-PLL than in CLL and this may reflect the aggressive nature of T-PLL.[2] T-cell CLL was used historically as a synonym for some small cell variants of T-PLL.[1] Most patients with T-PLL present with hepatosplenomegaly and generalized lymphadenopathy. Anemia and thrombocytopenia are common and the lymphocyte count is usually >100x10^9/L.[1] In the peripheral blood of our patient, we determined monoclonal CLL cells and 80% of all white blood cells were mature lymphocytes. However, in CSF, a few CLL cells were determined nearby numerous monoclonal T-PLL cells. Since the flow cytometric analysis of peripheral blood clonal lymphocytes and the clinical, and laboratory findings were not compatible with T-PLL, we assumed that a biclonal chronic lymphoproliferative disease developed in our patient. The excess T lymphocytes in CSF could be a reason of an inflammatory reaction due to some virus or opportunistic infections. However, this hypothesis is not supported by the other clinical and laboratory findings. Serological studies and cultures of CSF were all negative, CRP, procalcitonin levels were within normal limits at the time of diagnosis. On the other hand, the excess number of T lymphocytes was not accompanied by an increase in B lymphocytes, a finding expected in inflammatory processes. And also, the number of lymphocytes in CSF decreased by intrathecal chemotherapy. Additionally, CSF CD3 T-cells were TCR α/ß positive, but TCR ɣ/& negative; showing monoclonal origin, while peripheral blood T-cells were not monoclonal, since these CD3 cells were positive for both TCR α/ß and ɣ/&.

Flow cytometry was the main diagnostic method in our case. We could not show the clonality by molecular-genetic studies. However, molecular-genetic features can be used for the differential diagnosis of lymphoproliferative disorders, especially for T-PLL. In T-PLL; rearrangements involving TCL1 are common and relatively specific for T-PLL. These may take the form of either inv(14) or t(14;14)(q11;q32). Overall,

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approximately 80 percent of cases demonstrate chromosome abnormalities involving chromosome 14.[1] Abnormalities of chromosome 8, idic (8p11), t(8;8)(p11-12;q12) and trisomy 8q are seen in 70-80% of cases.[1] Deletions at 12p13 are also a feature of T-PLL when studied by FISH.[1] In CLL, molecular analysis [e.g., del(13q), del(17p)] can be used for the determination of prognosis and/or therapy, but not recommended as routine diagnostic tools.

Our case is the second one in the literature who was followed as CLL, but leptomeningeal infiltration developed due to clonal T-cells.[4] Primary meningeal lymphoma is a rare clinical entity. However, any neurological manifestation in CLL patients should arouse suspicion of meningeal leukemia and patients should be examined rapidly not only with serological, microbiological (cultures), biochemical tests, and radiological imaging techniques (especially cerebral MRI), but also cytological, immunocytochemical, and flow cytometry analysis should be done.[5-7] There is no standard treatment for this rare case. Traditionally, treatment has been based in craniospinal radiation therapy and intrathecal chemotherapy, with poor results. Systemic chemotherapy with high-dose methotrexate may be a good option to improve the prognosis of these patients.[7]

References

1. Swerdlow SH, et al. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. IARC Press, Lyon; 2008.
2. Watanabe N, et al. Excellent response of chemotherapy-resistant B-cell-type chronic lymphocytic leukemia with meningeal involvement to rituximab. Int J Clin Oncol. 2005;10:357-61.
3. Hanse MCJ, et al. Incidence of central nervous system involvement in chronic lymphocytic leukemia and outcome to treatment. J Neurol. 2008;225:828-30.
4. Remkova A, Bezayova T, Vyskocil M. B cell chronic lymphocytic leukemia with meningeal infiltration by t lymphocytes. Eur J Intern Med. 2003;14:49-52.
5. 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;99:775-8.
6. Kalac M, et al. Central nervous system involvement of previously undiagnosed chronic lymphocytic leukemia in a patient with neuroborreliosis. Int J Hematol. 2007;85:323-5.
7. Ponce J, et al. Primary meningeal lymphoma of T-cell origin: a rare presentation of primary central nervous system lymphomas. Clin Lymphoma Myeloma. 2007;7:546-9.

Information Presentation

Türk Hematoloji Derneği Kongresinde poster olarak sunulmuştur.