Clinical Case Reports

Open Access

CASE REPORT

Brain biopsy in the diagnosis of leptomeningeal involvement in stage I chronic lymphocytic leukemia

Eva Cervilla Muñoz[1], Pablo Demelo Rodríguez[1], Alejandra García García[1], Javier Menarguez Palanca[2] & Jorge del Toro Cervera[1]

[1]Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Department of Pathological Anatomy, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Correspondence
Eva Cervilla Muñoz, Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain.
Tel: +34678338919;
E-mail: cermuneva@gmail.com

Funding Information
No sources of funding were declared for this study

Received: 10 October 2016; Revised: 9 May 2017; Accepted: 27 May 2017

Clinical Case Reports **2017; 5(12): 1919–1922**

doi: 10.1002/ccr3.1106

Key Clinical Message

Leptomeningeal involvement of CLL is usually underdiagnosed as neurological symptoms are unspecific. It is important to carefully evaluate neurological status in these patients and consider this entity between the differential diagnosis of a neurological deterioration as adequate treatment improves the prognosis. Imaging techniques, analyses of cerebrospinal fluid, and brain biopsy are useful to establish a definitive diagnosis.

Keywords

Brain biopsy, chronic lymphocytic leukemia, hematology, leptomeningeal involvement.

Case Report

A 79-year-old woman was brought to our center because of acute confusional state and abnormal behavior. Patient relatives reported a two-month history of progressive disorientation, speech disorders, and visual hallucinations. Her medical history was remarkable for dyslipidemia, arterial hypertension, hypothyroidism, and chronic lymphocytic leukemia diagnosed 3 years earlier (Rai stage I/ Binet A). She received treatment with lorazepam, levothyroxine, omeprazole, simvastatin, and sertraline and did not receive any treatment for the CLL. Upon arriving at the hospital, neurological examination showed temporal disorientation, bradylalia, and unsteady walk. The rest of physical examination was normal. Cell blood count revealed leukocytosis (White blood count 43.800 10E3/μL, lymphocytes 89%), hemoglobin 12 g/L and 282 $\times$ 10^9 platelets/L. Biochemistry, including glucose, liver enzymes, renal function, sodium and potassium was normal. C-reactive protein was 1.8 mg/mL, and erythrocyte sedimentation rate was 51 mm/h. Peripheral blood smear showed lymphocytosis and Gumprecht shadows. The immunophenotypic analysis of peripheral blood confirmed the presence of 88% lymphocytes with pathological B immunophenotype *CD19+, CD5+, CD23+, CD20+ (weak), CD22+ (weak), light chain Lambda restriction, CD10, cyclin D1-, CD79b+(weak), FMC7-, CD38-, CD103-, CD11c-, CD25+ (weak), CD200++, ZAP70 –*, findings compatible with the previous diagnosis of CLL. FISH of the peripheral blood was negative for 17p13 deletion, 11q deletion, trisomy 12, 13q deletion. A computerized tomography (CT) of the brain showed hyperintensity and contrast uptake in the left temporoparietal area which was suggestive of leptomeningeal carcinomatosis (Fig. 1A). Magnetic resonance imaging (MRI) of the brain was performed, showing hyperintensity of signal in the left perirolandic and parieto-occipital areas as well as diffuse bilateral enhancement of the meningeal surface, confirming the presence of leptomeningeal infiltration (Fig. 1B). Full-body CT showed several abdominal lymphadenopathies with no other relevant findings. A CT-guided lumbar puncture was performed, obtaining a clear cerebrospinal fluid (CSF) with normal pressure. Gram stain of CSF was negative. Microbiological study of CSF

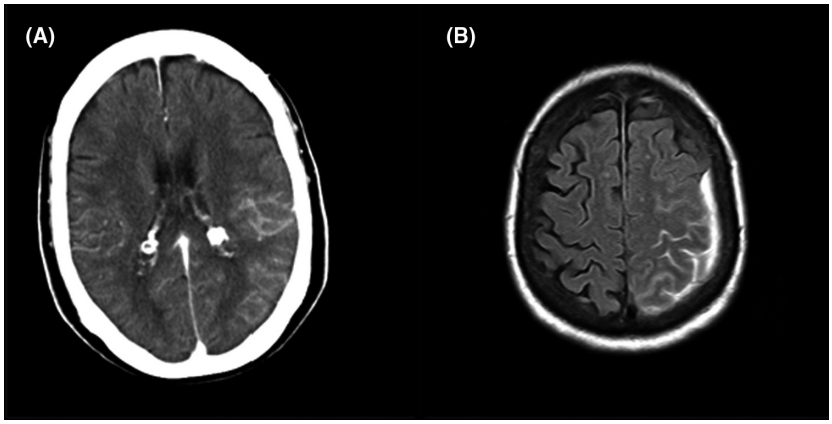

Figure 1. (A) CT scan showing hyperintensity in the left temporoparietal area. (B) Brain MRI: showing hyperintensity of signal in the left perirolandic and parieto-occipital area.

was negative for herpes simplex virus, varicella zoster virus, parvovirus, and polymerase chain reaction for fungi. Flow cytometry immunophenotyping of CSF showed 5% lymphocytes with the same characteristics of those from peripheral blood. However, due to the low percentage of cellularity compatible with CLL in CSF, it was considered contamination by peripheral blood. Further studies were accomplished, including upper endoscopy, colonoscopy, and mammography which were normal. A meningeal biopsy was performed, and the consequent anatomopathological study revealed meningeal and parenchymatous infiltration by CLL without evidence of transformation (Fig. 2).

Discussion

Chronic lymphocytic leukemia is a common lymphoproliferative disorder. It is more common among the elderly (with a median age at diagnosis of 70 years). CLL is characterized by accumulation of functionally incompetent monoclonal B lymphocytes. Patients are usually asymptomatic at diagnosis, and as the disease progresses, lymphocytes infiltrate lymph nodes, liver, and spleen. Leptomeningeal involvement is an uncommon initial presentation of untransformed CLL, with less than a hundred cases reported in the literature. The clinical manifestations are heterogeneous including headache, cranial nerve

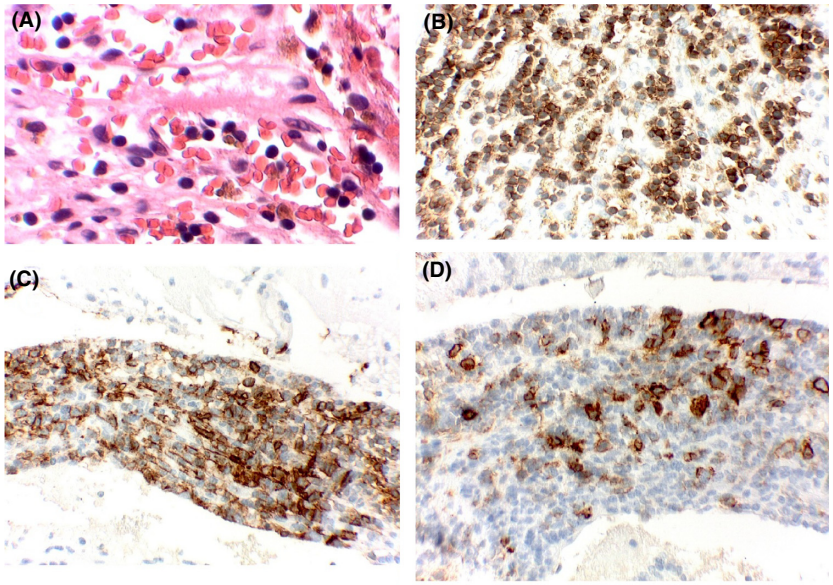

Figure 2. Biopsy specimens: (A) Hematoxylin–eosin protocol, showing an unspecific infiltration by small lymphocytes. (B) Positive immunohistochemistry for CD5, CD20 (C), and C23 (D).

palsies, cerebellar signs, visual alterations, ataxia, gait disturbances, or sensorimotor deficits. However, in many cases, patients remain asymptomatic, which leads to under-reported diagnosis. Several postmortem autopsy studies demonstrated the number of cases of CLL with CNS involvement is higher than reported, with a prevalence of 7–71% [1–4]. No relationship between leptomeningeal infiltration and the stage or time of evolution of CLL has been described. Likewise, risk or predisposing factors have not been identified [5].

Brain imaging (CT or MRI) have low sensitivity and specificity for the diagnosis of CNS involvement in CLL [5, 6]. Analysis of CSF in these patients includes global and specific cell count, glucose, proteins, and microbiological cultures [7]. CSF cytology is considered the "gold standard" due to its high specificity (>95%); however, it has low sensitivity (50–60%). This may be in part explained by the fact that morphologically, CLL lymphocytes cannot be distinguished from reactive lymphocytes [4]. For that reason, flow cytometry immunophenotyping (FCI) is also important in the diagnosis, with a higher sensitivity than cytology alone. FCI analysis of CSF enables identification of CLL-B lymphocytes expressing abnormal surface markers in CSF. Nevertheless, the results of FCI should be cautiously interpreted. The presence of monoclonal B cells in CSF may be due to the recruitment of these circulating malignant cells to the site of inflammation, in case another underlying condition is the cause of the neurological symptoms, such as infections or autoimmune/inflammatory diseases of CNS. In the same way, CLL-B lymphocytes could be found in CSF when a traumatic lumbar puncture is performed due to CSF contamination from peripheral blood. Therefore, the presence of CLL-B cells on CSF is not diagnostic of CNS involvement [7, 8].

Polymerase chain reaction is also useful for diagnosis, especially when it is combined with other techniques. It analyzes gene rearrangements of immunoglobulin heavy chain in the samples obtained from CSF, identifying whether the lymphocytes in CSF are the same as those from the CLL. It is particularly useful when the number of cells in CSF is low [9].

In our patient, a brain biopsy was needed for diagnosis as the results of cytomorphology and immunophenotype analysis were not conclusive. A recent study by Strati et al. showed 11% of CNS involvement by CLL in patients with evidence of brain lesion on MRI and negative results in CSF analysis [8]. In addition, among those patients with presence of CLL-B cells in CSF analysis, brain biopsy demonstrated in 58% of cases a different etiology for the neurological symptoms, such as infections, inflammatory processes, or metastatic cancer.

The treatment of patients with CLL and CNS involvement is not well defined. The standard treatment consists in the combination of radiotherapy, intrathecal, and systemic chemotherapy [4–6]. Although intrathecal chemotherapy is the most commonly used treatment, systemic regimens of chemotherapy with fludarabine have recently shown effectiveness. Drugs usually used for intrathecal chemotherapy include methotrexate, cytarabine, and corticosteroids. New lines of investigation include inhibitor of B-cell receptor, lenalidomide, or ibrutinib [8, 10].

Conclusion

In summary, CNS involvement by CLL is a rare condition that should be suspected in patients with CLL presenting with neurological symptoms. In symptomatic patients with negative results in imaging studies, CNS involvement of CLL should be suspected, and further studies, including analysis of CSF, should be accomplished. Cytomorphologic and immunophenotypic analyses of CSF are useful for diagnosis, but the results of these tests must be carefully interpreted. In this aspect, meningeal biopsy represents a useful tool in the diagnosis as it allows the direct visualization of CLL-B cells infiltration. Tissue biopsy is also useful to rule out other processes such as infections, inflammatory diseases, Richter syndrome, or metastasis from a solid tumor.

Authorship

JDTC and PDR: supervision and correction of the text. ECM and AGG: writers. JMP: anatomopathological study of samples.

Conflict of Interest

None declared.

Reference

1. Bojsen-Moller, M., and J. L. Nielsen. 1983. CNS involvement in leukaemia An autopsy study of 100 consecutive patients. Acta Pathol. Microbiol. Immunol. Scand A 91:209–216.
2. Barcos, M., W. Lane, G. A. Gomez, T. Han, A. Freeman, H. Preisler, et al. 1987. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 60:827–8373.
3. Cramer, S. C., J. A. Glaspy, J. T. Efird, and D. N. Louis. 1996. Chronic lymphocytic leukemia and the central nervous system: a clinical and pathological study. Neurology 46:19–25.

4. Morrison, C., S. Shah, and I. W. Flinn. 1998. Leptomeningeal involvement in chronic lymphocytic leukemia. Cancer Pract. 6:223–228.
5. Lima de Souza, S., F. Santiago, M. Ribeiro-Carvalho, A. Arnóbio, A. Ribeiro Soares, and M. H. Ornellas. 2014. Leptomeningeal involvement in B-cell chronic lymphocytic leukemia: a case report and review of the literature. BMC Res. Notes 7:645.
6. Benjamini, O., P. Jain, E. Schlette, J. S. Sciffman, Z. Estrov, and M. Keating. 2013. Chronic lymphocytic leukemia with central nervous system involvement: a high-risk disease? Clin. Lymphoma Myeloma Leuk. 13:338–341.
7. Nowakowski, G. S., T. G. Call, W. G. Morice, P. J. Kurtin, R. J. Cook, and C. S. Zent. 2005. Clinical significance of monoclonal B cells in cerebrospinal fluid. Cytometry B Clin. Cytom. 63:23–27.
8. Strati, P., J. H. Uhm, T. J. Kaufmann, C. Nabhan, S. A. Parikh, C. A. Hanson, et al. 2016. Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia. Haematologica 101:458–465.
9. Garicochea, B., M. G. Cliquet, N. Melo, A. del Giglio, P. E. Dorlhiac-Llacer, and D. A. Chamone. 1997. Leptomeningeal involvement in chronic lymphocytic leukemia identified by polymerase chain reaction in stored slides: a case report. Mod. Pathol. 10:500–503.
10. Tam, C. S., T. Kimber, and J. F. Seymour. 2016. Ibrutinib monotherapy as effective treatment of central nervous system involvement by chronic lymphocytic leukaemia. Br J Haematol 176:829–831.