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

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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 x 10⁹ 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 perirlandic 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
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...
Brain involvement in chronic lymphocytic leukemia

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.

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