Bilateral Occipital Lobe Invasion in Chronic Lymphocytic Leukemia

In October 2004, a 58-year-old, alcoholic Japanese man was referred to our hospital with a temporary seizure. He also had a history of leukocytosis for about 10 years without any therapeutic agents, and chronic inflammatory disorders. His WBC counts were $36 \times 10^3$/$\mu$L, hemoglobin level was 10.0g/dL, and platelet counts were $11.2 \times 10^3$/$\mu$L. The leukocytosis was almost entirely comprised of small round mature lymphocytes with scant cytoplasm. The cell surface markers of these lymphocytes were examined and were positive for CD5, CD19, CD20, and negative for CD10, unfortunately CD23 was not examined and the patient declined to undergo a bone marrow examination. We diagnosed as Rai stage III chronic lymphocytic leukemia (CLL) and a blood analysis was performed regularly each month. In January 2005, he was admitted to our hospital again because due to a poor memory and progressive blindness. No significant changes were seen in the size of the lymphadenopathy, and no increased number of prolymphocytes and no infiltration of large lymphoid cells were seen in the peripheral blood. A lumbar puncture was performed and no CLL cells were found to have infiltrated the CSF. Brain magnetic resonance imaging (MRI) was performed immediately; a T2 high signal intensity lesion was described in the bilateral occipital lobe (Fig 1A). As for the differential diagnosis, we considered reversible posterior leukoencephalopathy syndrome (RPLS) and expected the lesion to improve naturally. But, 1 month later his symptoms were progressive and the occipital lobe lesions in the brain were widely spread, as displayed by brain MRI (Fig 1B). An open brain biopsy was performed to establish the diagnosis. Small round mature lymphocytes were infiltrated diffusely in the meninges and brain, moreover these lymphocytes were positive for CD79a with increased fibers by immunostain and silver stain both meninges (Figs 2A to 2C) and brain (Figs 2D to 2F). These lymphocytes were negative for CD3, CD5, CD10, CD23, and cyclinD1 by immunostain. We diagnosed the patient as having direct meningeal and cerebral invasion of CLL. The patient received an intermediate dose of intravenous (IV) methotrexate (MTX; 30 mg/kg/d at day1) injection and next, IV fludarabine phosphate (25 mg/m² at 5 days), again an intermediate dose of IV MTX (100 mg/kg/d at day 1) injection and finally cranial radiation (total dose of 30 Gy) was performed, but all treatment was ineffective and the patient died 6 months after receiving chemotherapy.

CLL is the most common type of leukemia in North America and Europe. However, it is rare in the Far East. The involvement of extranodal sites such as the skin, liver, spleen, and other organs are common in CLL, but CNS and leptomeningeal involvement are very rare. Some reports have shown that progressive disease states, such as prolymphocytic leukemia and Richter’s syndrome, are considered as possibly predisposing to meningeal infiltration. However, invasion of the CNS in patients with CLL has been reported even in early-stage CLL. CNS involvement in CLL is not uncommon in some autopsy reports. In fact, Barcos et al reported that the percentage of CNS involvement in the brain, dura mater and leptomeningeal were 7%, 21%, and 8%, respectively, in their autopsy study. Cramer et al reviewed the neuropathologic findings of 12 autopsy cases with
CLL and the clinical characteristics of 21 patients with CLL with CNS involvement at Massachusetts General Hospital (Boston, MA). They described the symptomatic infiltration of the CNS by CLL as uncommon and usually expressed it as a confusional state, meningitis with cranial nerve abnormalities, optic neuropathy, or cerebellar signs. However, no mention of CNS involvement in CLL is to be found in any textbooks of clinical hematology, except in regard to refractory CLL. Therefore, a careful consideration of the initial diagnosis is required, if patients with CLL present with neurologic findings.

The diagnosis of CNS involvement by CLL is established by finding CLL cells in the CSF. A traumatic puncture should be avoided because of peripheral blood contamination. If a brain space-occupied lesion is detected in CLL, the brain mass is spreading and/or CNS symptoms are progressive, then a lumbar puncture should be repeated and consideration given to a brain biopsy which may be required to achieve a precise diagnosis. Our review of the literature (data not shown, from 1986 to 2008) showed 25 cases of CLL patients with CNS involvement. The time to CNS involvement varies, and it ranges from the time of the initial presentation to 14 years after the first diagnosis. Nine cases were early-stage CLL at the time of the CNS involvement and 11 cases were advanced stage. Only five cases (one case was autopsy) showed brain mass on computed tomography/MRI without infiltration in the CSF. In our case, no CLL cells were seen in CSF examination, although they were detected in the meninges when the brain was biopsied.

The intrathecal MTX injection and cranial radiation are recommended as sensitive therapies for CNS involvement by CLL. In contrast, systemic chemotherapy was administered in only 4 cases and three patients received fludarabine phosphate. One patient received chlorambucil. In contrast, an intrathecal injection of MTX seems to be effective, however, an appropriate systemic treatment for CNS involvement with CLL is still remains to be established.

We showed CNS involvement in this case occurred as a direct meningeal and bilateral occipital lobe invasion of the brain in a patient with CLL. It was necessary to discriminate the brain mass between a CLL invasion, some other malignancy or RPLS in our case. RPLS is a subacute neurological syndrome typically which normally manifests with such symptoms as headache, blindness, and seizures, and it is also associated with risk factors such as malignant hypertension, eclampsia, and renal failure. Numerous cases of RPLS have been reported in patients with cancer who were receiving chemotherapeutic agents. Although this patient did not receive any cytotoxic chemotherapy before diagnosis, the brain lesion was suspected to have been due to RPLS because of the clinical symptoms and MRI findings. There was, however, no explanation as to why the brain mass was spreading bilaterally in the occipital lobe of the brain. No reports have ever previously described such RPLS-like CNS invasion in patients with CLL. This patient showed no improvement naturally and, therefore, an open brain biopsy was performed, finally resulting in the precise diagnosis. Although CNS involvement, especially direct cerebral invasion at initial presentation is extremely rare, it should therefore be carefully considered.

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REFERENCES

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