Epstein-Barr Virus–Associated CD3⁻ Large Granular Lymphocyte Leukemia Presenting With Polycranial Nerve Palsies

To the Editor:

A clinical entitity of large granular lymphocyte (LGL) leukemia was established based on the observation of clonality and the demonstration of tissue invasion by LGL of marrow, spleen, and liver.[1] The clonal expansion of LGL can be divided into two major lineages: $CD3^+$ and $CD3^-$ (natural killer: NK); however, it is still difficult to prove clonality in $CD3^-$ NK LGL proliferation because $CD3^-$ cells do not express the CD3/T-cell receptor (TCR) complex or rearrange TCR genes.[2] Usually an immediate diagnosis of $CD3^-$ NK LGL leukemia has been made by the clinical manifestation such as an extreme increase of $CD3^-$ LGL in blood and marrow, lymphadenopathy, hepatosplenomegaly, and other invasive symptoms. We present a case with $CD3^-$ NK LGL proliferation only in cerebrospinal fluid (CSF), which did not have any leukemic features but only polycranial nerve palsies and could not be distinguished from the reactive LGL proliferation until a systemic leukemic progression occurred later. The clonality of LGL from this case was proven finally by analyzing the polymorphic fused termini of Epstein-Barr viral (EBV) genome.[3]

CASE REPORT

A 34 year-old Japanese man was referred to us because of right facial palsy, double vision, and left hearing loss on October 29, 1992. These symptoms began in early September 1992 with slight fever and painful neck lymphadenitis. Polycranial nerve palsies progressed slowly, whereas fever and lymphadenitis disappeared quickly. He had neither fever nor lymphadenopathy on admission. No hepatosplenomegaly was noted. The CSF test was as follows: cell count 861/3 with mainly LGL, total protein 52.2 mg/dL, sugar 24 mg/dL, chloride 110 mEq/L, and negative tryptophan test. No micro-organisms, including mycobacterium tuberculosis and cryptococcus, were detected. Surface marker analysis of cells from the CSF was as follows: CD2 99.4%, CD3 0.3%, CD4 0.6%, CD8 97.4%, CD56 98.7%, and HLA-DR 94.3%. Neither anemia nor thrombocytopenia were noted. White blood cell count was 5.3×10^9/L with a normal differential. No LGL was detected in the blood or marrow. No abnormal findings in serum chemistry including lactic dehydrogenase, were noted. Radiologic study of brain by computed tomography (CT) and magnetic resonance imaging (MRI) was negative. Both antinuclear and anti-DNA auto antibodies were negative. Although these $CD3^-$, $CD8^+$, $CD56^+$ phenotypically monoclonal LGL were increased in the CSF, leukemic meningeal infiltration could not be distinguished from a reactive proliferation at this time.

Severe dyspnea and high fever developed suddenly on November 24, 1992. Metabolic acidosis, pleural effusion, and hepatosplenomegaly appeared simultaneously. As the LGL in the pleural effusion had the same surface markers as those in the CSF, NK LGL leukemia was diagnosed. Although multiagent chemotherapy with intrathecal administration were repeated intensively, the patient died of multiorgan failure, probably due to the systemic NK LGL infiltration, on January 12, 1993. LGL, with the same surface markers as observed in prior test of the CSF and pleural effusion, appeared in the blood for the first time only on the final day. Necropsied specimens ob-

tained from liver, spleen, and bone marrow showed a diffuse infiltration of leukemic cells. Immunochemical histologic study of the liver sections showed $CD56^+$ leukemic cells infiltrating mainly in the portal areas. In situ RNA-RNA hybridization[4] showed the direct evidence for the presence of EBV within the infiltrated leukemic cells. Southern blot analysis of genomic DNA obtained from the necropsied liver for TCR-β, TCR-γ and Ig chains[5] revealed retention of germ line configuration. The hybridization analysis of the genomic DNA with a probe specific for one of the termini of the EBV genome[3] showed a single band indicating clonality of the NK LGL.

DISCUSSION

Common clinical and hematologic features in NK LGL leukemia have been reported as the following: (1) high fever without signs of infection and other B symptoms; (2) neutropenia; (3) anemia; (4) lymphocytosis; (5) massive hepato-splenomegaly; (6) involvement of the gastrointestinal system with jaundice and ascites; and (7) hypergammaglobulinemia.[1] This is the first report of a case that presented only meningeal infiltration without any other apparent systemic involvement or leukemic symptoms. Although a Japanese case showed meningeal infiltration with facial nerve palsy in an advanced stage of NK LGL leukemia, it was accompanied by many other leukemic features at the same time.[6]

Some reports have indicated that some patients with NK LGL leukemia may have a chronic phase before acute transformation. Although the clinical course of the present case is very similar to those reported, and additional clonal evolution was suspected, surface marker analysis showed no difference before and after the systemic leukemic progression. The number of NK LGL was too low for a chromosome analysis and other cytogenetic studies before the systemic involvement.

The presence of EBV genome in NK LGL and a single band for the joined termini of the EBV genome were clearly demonstrated in this patient. These findings indicate not only a neoplastic clonality but also a possible oncogenic role of EBV which could be contributing to the evolution of the NK LGL leukemic clone. When EBV is involved in the development of NK LGL leukemia, an EBV DNA integration study may be very useful for proving clonality in the clinical setting. However, NK LGL leukemia in a significant number of patients has not been associated with EBV and it is still difficult to make a diagnosis of NK LGL leukemia without any invasive findings at an early stage of the disease.[7] Further studies including new methods are needed to determine clonality and to make an immediate diagnosis of NK LGL leukemia.

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