Human T-Cell Lymphotropic Virus Type-I (HTLV-I)-Associated Myelopathy/Tropical Spastic Paraparesis with Acute Type of Adult T-Cell Leukemia

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We report a 47-year-old Japanese woman with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) combined with acute type adult T-cell leukemia (ATL). The susceptibility for HAM/TSP and acute type of ATL is hitherto explained by human leukocyte antigen (HLA) haplotype-linked immune responsiveness to HTLV-I. This patient’s HLA (A24/Cw1B54DR4DQ4/A24/Cw3B51DR8DQ1) included a HAM-associated HLA haplotype. This suggests that HAM patients with HAM-associated HLA haplotype can also develop the acute type of ATL.

[Internal Medicine 34: 1130-1133, 1995]

Key words: HLA haplotype, southern blot analysis, autopsy

Introduction

Human T-cell lymphotropic virus type-I (HTLV-I) is an etiologic agent for both HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (1) and adult T-cell leukemia (ATL) (2). Since a single species of HTLV-I has been identified as the etiologic agent for both HAM/TSP and ATL (3), the susceptibility for HAM/TSP and acute type of ATL is hitherto explained by human leukocyte antigen (HLA) haplotype-linked immune responsiveness to HTLV-I. Actually some cases of HAM/TSP patients with chronic or smoldering type of ATL have been reported (4-8), but the combination of HAM/TSP and acute type of ATL is rare (9, 10). These previously reported HAM with acute or lymphoma type of ATL cases were not examined for the HLA haplotype. We report a case of HAM/TSP with acute type ATL confirmed by Southern blot analysis, and show that this patient had HLA haplotype (A24/Cw1B54DR4DQ4/A24/Cw3B51DR8DQ1) which is a common haplotype for HAM/TSP patients and not for acute type ATL.

Case Report

A 47-year-old Japanese woman noticed paraparesis in 1971 when she was 26 years old. Her gait disturbance slowly progressed, and she was admitted to Kagoshima University Hospital in 1986 at the age of 42. At that time her leukocyte count was 6,000/μl with 61% lymphocytes without morphological abnormality, and the serum lactate dehydrogenase (LDH) level was normal. Physical examination revealed no lymph node swelling nor hepatosplenomegaly. Neurological examination showed marked spasticity and hyperreflexia with mild sensory disturbance of lower extremities, and urinary bladder disturbances. Other neurological findings involving consciousness, cranial nerve signs and upper extremities were normal. The HTLV-I antibody titer as measured by particular agglutination test was increased to 8,192× in the serum and was 256× in the cerebrospinal fluid (CSF). She was diagnosed as HAM/TSP; prednisolone was administered with temporal improvement of gait disturbance. Southern blot analysis of DNA from peripheral blood lymphocytes at that time showed an increased amount of HTLV-I infected lymphocytes with monoclonal proliferation (Fig. 1). A careful follow-up could not be performed because she did not consult the hospital.

Five years later in November 1991, she was admitted to our hospital with fever, cervical lymphadenopathy and abdominal distension. On physical examination, body temperature was 37.3°C and the chest was clear to percussion and auscultation. Lymphadenopathy of the left neck (3×3cm), the right axilla (2×2cm), and both inguinal regions (2×1cm) was observed.
HAM with Acute ATL

Hepatosplenomegaly was not found but ascitis was observed. Neurological examination revealed almost identical symptoms with that of 5 years before, gait disturbance with marked spasticity and hyperreflexia of lower extremities with bilateral Babinski’s sign, mild sensory disturbance (touch and vibration) of lower extremities, and urinary bladder disturbance. Other neurological findings involving consciousness, cranial nerve signs and upper extremities were normal.

Laboratory test data on peripheral blood were: Hemoglobin (Hb), 10.8g/dl; Red blood cell count (RBC), 432×10^6/μl; White blood cell count (WBC), 10,200/μl with 80.5% neutrophils, 8% lymphocytes, 1.5% atypical lymphocytes, 9% monocytes, 0.5% basophils, and 0.5% eosinophils; platelet 26.7×10^4/μl. Her serum LDH level was 1,701 W.U./l and calcium was 4.0 mEq/l. Examination of lymphocyte subsets in the peripheral blood showed 64.1% CD3+, 41.2% CD4+, and 27.6% CD8+; CD4+/CD8+ ratio: 1.49. The HTLV-I antibody titer by particle agglutination test was increased to 2,048× in the serum. Her HLA haplotype was determined as A24Cw1B54DR4DQ4/ A24Cw3B51DR8DQ1. An X-ray film of the chest revealed dullness of right costophrenic angle. A computerized tomography scan of the chest and abdomen revealed pleural effusion, ascitis, retroperitoneal mass and lymphadenopathy of paraaortic lesion. Bronchoscopy was performed and the laboratory data of bronchoalveolar lavage fluid (BALF) showed 0.5% neutrophil, 32% lymphocyte, 6.5% monocyte cell and 61.5% histiocyte. There were no neoplastic cells in the BALF. Abdominal puncture was performed and the laboratory data obtained from the ascitis were 1.5% neutrophil, 14% lymphocyte, 13.5% monocyte cell, 10.5% mesothelial cell and 60.5% abnormal lymphoid cells having convoluted nuclei. CT findings of the brain revealed no apparent central nervous system (CNS) involvement, and thus lumbar puncture was not performed to prevent the injection of ATL cells to CNS from peripheral blood. Biopsy of the swollen cervical node revealed pleomorphic type of non Hodgkin’s lymphoma which is compatible with ATL. The Southern blot analysis of DNA in the patient’s peripheral blood lymphocytes showed that HTLV-I infected lymphocytes proliferated monoclonally which seemed to be the same clone as that of five years before as judged from the electrophoretic mobility of the bands (Fig. 1). This patient had tumor lesions of lymph node and ascitis with ATL cells, and the serum LDH level was more than 2-fold the normal range, and it harbored more than 1% abnormal lymphocytes in total WBC, which fulfilled the diagnosis of acute type of ATL based on the criteria proposed by Shimoyama (11). A combined chemotherapy resolved lymphadenopathy, pleural effusions, and abdominal distension. In January 1992, the above symptoms recurred and chemotherapy was not effective. In May 1992, jaundice, melena, cachexia, and disseminated intravascular coagulation (DIC) developed, her serum calcium on May 16 was 8.2 mEq/l. Laboratory data on May 22 of peripheral blood were: Hb, 10.0g/dl; RBC, 311×10^6/μl; WBC, 47,200/μl with 47% neutrophils, 0.5% lymphocytes, 5% monocytes, 0.5% basophils, and 47% of ATL cells; platelet 5.2×10^4/μl. Her serum LDH level was 4857 W.U./l and calcium was 5.6 mEq/l; she died on May 22. Autopsy finding revealed adult T cell leukaemia-lymphoma, involving lymph nodes of cervical, mediastinal, perigastric, peripancreatic, mesenteric and iliac regions. ATL had also invaded the lungs, liver, spleen, adrenal glands, terminal ileum, colon, kidneys, and bone marrow. In addition, unrecognized acute hemorrhagic pancreatitis was found. Hypercalcemia due to ATL is attributable to the genesis of the pancreatitis. Southern blot analysis of DNA of her lymph node frozen at the time of autopsy revealed that the same clone as in her peripheral blood 5 years before had proliferated monoclonally (Fig. 1). Leukemic infiltration was not found in the central nervous system. The spinal cord showed marked atrophy at the thoracic level. Histologically marked loss of axon and myelin, and hyaline vascular thickening without lymphocytic infiltration were found in the lateral and anterolateral column of the spinal cord, especially in the thoracic segment (Fig. 2).

Figure 1. DNA blot analysis of the HTLV-I proviral genome in peripheral blood lymphocytes (left and middle column) and lymph node (right column). Ten micrograms of cellular DNA were digested with Pst I and subjected to standard Southern blot procedure. The filter was hybridized with a total HTLV-I probe (lane a) and then with a LTR probe (lane b). Numbers at the bottom of the columns represent date of samples collected. Arrowheads show the viral-cellular junction bands with LTR probe, in addition to three internal bands (2.5kb, 1.8kb, 1.2kb).

Internal Medicine Vol. 34, No. 11 (November 1995)
Discussion

In 1986, at the age of 42, the present patient fulfilled the diagnostic criteria of HAM/TSP developed by Osame (12), having chronic progressive spastic paraparesis, positive HTLV-I antibody both in blood and spinal fluid, and no findings of possible compression of the spinal cord. Although southern blot analysis revealed monoclonal proliferation of HTLV-I infected lymphocytes, we could not diagnose that this patient had ATL, because there were no signs of ATL (e.g. lymph node swelling, skin symptom, hepatosplenomegaly, lung invasion), and Ikeda et al reported that there are healthy HTLV-I carriers having monoclonally proliferated HTLV-I infected lymphocytes (8). Five years later, she had tumor lesions of lymph node and ascitis with ATL cells, and serum LDH level was more than 2-fold the normal range, and harbored abnormal lymphocytes of more than 1% of peripheral blood leukocyte, which fulfilled the diagnosis of acute type of ATL based on the criteria proposed by Shimoyama (11). But HAM/TSP symptoms did not worsen. HAM/TSP symptoms did not change when ATL symptoms were resolved with chemotherapy. The autopsy findings showed no leukemic infiltration in the central nervous system. The thoracic segment of the spinal cord, showed sections with the characteristic findings for the chronic phase of HAM/TSP (13). These findings strongly support the notion that ATL and HAM/TSP are different clinical entities, though both diseases are closely associated with HTLV-I infection.

Clonal proliferation of HTLV-I infected lymphocytes in HAM/TSP patient is not rare (14). In the present patient, the clonal patterns of HTLV-I infected peripheral blood lymphocytes at the times of HAM/TSP only, when ATL developed, and those of the lymph node at the time of autopsy were the same. This fact may suggest a multistep leukemogenesis of ATL. The clonally proliferated HTLV-I infected lymphocytes were benign in 1971 when she had only HAM/TSP symptoms, and some additional mutation may have caused a malignant transformation in this clone which then developed into acute type of ATL.

Since a single species of HTLV-I has been identified as the etiologic agent for both HAM/TSP and ATL (3), Usuku et al suggested that HLA haplotype-linked immune responsiveness to HTLV-I may explain susceptibility to HAM/TSP and ATL (15). In acute or lymphoma type of ATL, A26Cw3Bw62DR5-DQw3 is associated. The HLA haplotypes observed in HAM/TSP patients are A24Cw7Bw7DR1DQw1, A24Cw-Bw52DR2-DQw1, A11Cw1Bw54DR4DQw4, A24Cw1Bw54DR4DQw4, A2Cw7Bw60DRw8DQw1, and are linked with HAM/TSP as

Table 1. Previous Reports of HAM/TSP with ATL

<table>
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<tr>
<th>Age</th>
<th>Sex</th>
<th>Clinical course</th>
<th>Type of ATL</th>
<th>HLA</th>
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<td>42</td>
<td>F</td>
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<td>A2A11Cw1Cw3Bw22Bw46</td>
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<td></td>
<td>A24Cw3B-DR4DQwa</td>
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<tr>
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<td>#9</td>
</tr>
<tr>
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<td>M</td>
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<td>lymphoma</td>
<td>Not described</td>
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</tbody>
</table>
HAM with Acute ATL

well with chronic or smoldering ATL. Actually 6 cases of HAM/TSP with chronic or smoldering type of ATL have been reported (4-8). But only 2 cases of HAM/TSP patients with acute or lymphoma type of ATL have been reported (9, 10) (Table 1). These previously reported HAM/TSP cases with acute or lymphoma type of ATL were not examined for the HLA haplotype. We could examine the HLA haplotype of the patient in this report. In spite of the HLA haplotype (A24Cw1B54DR4DQ4/A24Cw3B51DR8DQ1) which are common haplotypes for HAM/TSP patients and not for acute type of ATL, the present patient developed the acute type of ATL. This suggests that HAM patients with HAM-associated HLA haplotypes can also develop the acute type of ATL. HAM/TSP patients with clonal proliferation of HTLV-I infected lymphocytes must then be carefully monitored.

References