

Clinical Diversity in Adult T-Cell Leukemia-Lymphoma¹

Kiyoshi Takatsuki, Kazunari Yamaguchi, Fumio Kawano, Toshio Hattori, Hiromichi Nishimura, Hiroyuki Tsuda, Isao Sanada, Kiyonobu Nakada, and Yayeko Itai

The Second Department of Internal Medicine, Kumamoto University Medical School, Honjo, Kumamoto 860 [K. T., K. Y., F. K., T. H., H. N., H. T., I. S.]; Okinawa Kyodo Hospital, Itoman, Okinawa 901-03 [K. N.]; and Minamata Kyoritsu Hospital, Minamata, Kumamoto 867 [Y. I.], Japan

Abstract

Adult T-cell leukemia-lymphoma (ATL) is a unique T-cell cancer first described in Japan. We estimate that more than 200 patients a year have been detected in Kyushu. The surface phenotype of ATL cells characterized by monoclonal antibodies is T3⁺, T4⁺, T8⁻, T11⁺, and Tac⁺. In all cases the serum is positive for anti-human T-cell leukemia (lymphotropic) virus (HTLV-I) antibodies and the ATL cells contain the proviral DNA of HTLV-I. Variations in the clinical features of atypical cases suggest a division of the spectrum of ATL into five types: acute (prototypic), chronic, smoldering, crisis, and lymphoma. Screening of the sera from healthy adults for presence of the anti-HTLV-I antibodies revealed that 3.6% of healthy individuals in Kumamoto Prefecture, which is located in the middle of Kyushu, were HTLV-I carriers. The percentage of positivity increased with age and was higher in females than in males. It varied from town to town, ranging from 0 to 17.6%. Family studies showed that the routes of natural infection of HTLV-I are from mother to child and also from husband to wife. The third route is blood transfusion. The borderline between the healthy carrier state and smoldering ATL remains unclear. In the endemic areas smoldering ATL is frequently diagnosed in patients with fungus infection of the skin, chronic lymphadenopathy, interstitial pneumonitis, chronic renal failure, and stronglyloidiasis. In addition our experiences with a concurrence of lymphoma-type ATL in three sisters and spontaneous remissions in a patient with chronic ATL are cited.

Introduction: Prototypic ATL²

ATL shares some features with Sézary syndrome but is distinct from it. Takatsuki *et al.* (1) studied 35 patients in Kyoto and described the following findings. In 18 males and 17 females, the age at the onset ranged from 27 to 73 years, with a median age of 52 years. The predominant physical findings were peripheral lymph node enlargement (86%), hepatomegaly (72%), splenomegaly (51%), and skin lesions (49%). The WBC ranged from 10,000 to 500,000. Leukemic cells resemble Sézary cells, having indented or lobulated nuclei. The surface phenotype of ATL cells characterized by monoclonal antibodies is T3⁺, T4⁺, T8⁻, T11⁺, and Tac⁺ (2). Hypercalcemia is frequently associated with this condition. Regarding skin lesions, one of the characteristic manifestations of this disease, histological examination revealed that dermal and s.c. infiltration was common and that epidermal infiltration, like a Pautrier's microabscess, was found frequently. The survival time ranged from 1 month to more than 6 years. The most striking aspect in our study was the clustering of the

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² The abbreviations used are: ATL, adult T-cell leukemia-lymphoma; HTLV-I, human T-cell leukemia-lymphotropic virus I.

patients' birthplaces; 22 of 35 were born in Kyushu, 11 of them in Kagoshima Prefecture. Most of them had grown up in their places of birth and moved later to their present locations. This peculiar geographical distribution led us to consider this leukemia to be a new disease. Subsequently it has become necessary to reexamine the concept of ATL in the light of new virological evidence.

Variations in the Clinical Course of ATL

Seventy-two patients with ATL have been examined in our department. Variations in the clinical features of atypical ATL suggested a division of the spectrum of ATL into five types: acute (39 patients); chronic (12 patients); smoldering (8 patients); crisis (5 patients); and lymphoma (8 patients). In all cases the serum was positive for anti-HTLV-I antibodies and the monoclonal integration of proviral DNA of HTLV-I in the malignant cells was confirmed as described later.

The acute type is the so-called prototypic ATL, which progresses acutely or subacutely. In general a poor prognosis is indicated by the elevation of serum lactate dehydrogenase, calcium, and bilirubin, as well as by high WBC. Smoldering ATL is characterized by the presence of a few abnormal cells (0.5-3%) in the peripheral blood over a long period. Crisis in chronic or smoldering ATL means the progression of the disease to acute ATL. The lymphoma type of ATL is considered to be a form of T-cell-type non-Hodgkin's lymphoma in which malignant cells contain proviral DNA of HTLV-I.

Detection of HTLV-I Proviral DNA

HTLV-I proviral DNA integrated in the cellular DNA was examined by the Southern blotting method in the peripheral blood mononuclear cells and/or lymph node cells from patients with ATL and other various hematological disorders (3). This study was carried out in collaboration with Dr. Mitsuaki Yoshida and his coworkers in the Department of Viral Oncology, Cancer Institute, Tokyo, Japan. In all ATL cases anti-HTLV-I antibody in the serum and proviral DNA in the malignant cells have been detected. No discrepancy was seen in the pattern of proviral DNA among tumor cells of peripheral blood and lymph node cells from the same patient. Proviral DNA was clearly demonstrated in peripheral blood cells from smoldering ATL patients, although the quantities were less than those from acute or chronic ATL. In addition proviral DNA was detected in lymph node cells of some cases clinically diagnosed as malignant lymphoma. Of 16 non-Hodgkin's lymphoma cases, 5 cases belonged to the T-cell type, 8 to the B-cell type, and 3 to the null-cell type. Anti-HTLV-I antibody was found in four cases of the T-cell type, two cases of the B-cell type, and one case of Hodgkin's disease. However, proviral DNA was detected in three cases of non-Hodgkin's

diffuse lymphoma of the T-cell type. In four cases positive for anti-HTLV-I antibody proviral DNA was not detected, suggesting that despite infection with HTLV-I this virus had not caused the tumor. It was difficult to distinguish between HTLV-I-related T-cell-type malignant lymphoma and non-HTLV-I-related T-cell malignant lymphoma, either histologically or immunologically. Checking for anti-HTLV-I antibody alone in endemic areas, such as Kyushu, is not sufficient to confirm a diagnosis of ATL. In the so-called nonleukemic malignant lymphoma abnormal cells were not seen in peripheral blood, but the presence of HTLV-I was verified. Accordingly this may be more appropriately called "lymphoma-type ATL" as discussed before.

The presence of proviral DNA in the peripheral blood was also tested in 15 cases of various leukemias other than ATL. Among these, four anti-HTLV-I antibody-positive cases had received large and frequent blood transfusions, and it is thought that seroconversion was due to this fact. However, proviral DNA was found in none of the cases. In Sézary syndrome and T-cell chronic lymphocytic leukemia, tests for anti-HTLV-I antibody and proviral DNA were negative. The causes of disease in these cases are thought to differ from those in ATL patients.

In family members of ATL patients anti-HTLV-I antibody in serum and proviral DNA in the peripheral blood lymphocytes were surveyed. Eight of 26 persons were anti-HTLV-I antibody positive. This rate was far higher than the average for healthy adults over 40 years old in Kyushu, but proviral DNA was not detected in any of them.

Seroepidemiology of HTLV-I

Anti-HTLV-I antibodies were examined by an indirect immunofluorescence test using the MT-1 cultured cell line as target cells (4). In 13,329 healthy adults inhabiting Kumamoto Prefecture 3.6% were found to be positive for these antibodies. The rate of positivity gradually increased with age and was higher in females than in males. With regard to geographical distribution the percentage of positivity varied from town to town, ranging from 0 to 17.6%. The family studies suggested two main routes of transmission of HTLV-I: one vertical from mother to children; and the other horizontal from husband to wife. The third route is blood transfusion.

Smoldering ATL

The borderline between healthy carriers of HTLV-I and patients with smoldering ATL is vague because the Southern blotting method of detecting monoclonal integration of proviral DNA of HTLV-I is not sensitive enough in the specimen from individuals with few abnormal cells in the peripheral blood. In our study smoldering ATL has been found frequently in patients with skin mycosis (fungus infection of the skin), slight lymphadenopathy in which biopsy shows chronic lymphadenitis, abnormal lung X-ray shadows resembling interstitial pneumonitis,³ chronic renal failure, and strongyloidiasis (5). Thus smoldering ATL is considered to be associated with an immune deficiency state to some extent.

³ Y. Itai, S. Kamizikoku, S-Y. Lee, S. Tomino, K. Yamaguchi, and K. Takatsuki. Interstitial pneumonitis and smoldering adult T-cell leukemia, submitted for publication.

We have also noticed that the association of monoclonal gammopathy and other neoplasms is significantly more frequent.

Unusual Cases of ATL

Concurrence of Lymphoma-type ATL in Three Sisters.⁴ We studied three sisters, ranging from 56 to 59 years old, who developed lymphoma-type ATL during a period of 19 months. The patients were born in a remote island in Kumamoto Prefecture, an area where the incidence of ATL is high, but had lived in different places since their youth, suggesting that the disease developed after a long latent period regardless of their living environments.

Spontaneous Remissions in ATL (6). We reported a 54-year-old male patient with ATL who had showed five episodes of exacerbation during a period of 6 years. In this case spontaneous remission occurred at least twice.

Cytogenetic Study

Specific chromosomal abnormalities analogous to those of the Philadelphia chromosome in chronic myeloid leukemia have not been found in any of the lymphocytic leukemias. We studied 13 patients with ATL in Kyoto (7) and 18 patients in Kumamoto (8). In the latter study the patients were divided into three groups according to their clinical manifestations; nine had acute, six chronic, and three smoldering ATL. Mitotic cells were obtained from peripheral blood, lymph node, or bone marrow and were analyzed by the G-banding technique. In acute ATL the chromosome number ranged from diploid or pseudodiploid to hyperdiploid, in the chronic type it ranged from hypodiploid to hyperdiploid, but in the smoldering type it was diploid. Eight of nine patients with acute ATL had trisomy 3 and/or trisomy 7, whereas none of the those with chronic ATL exhibited these aberrations. Patients with smoldering ATL had a normal karyotype. These findings indicate that the more aggressive the clinical course of ATL, the more complicated is the numerical and structural chromosome abnormality.

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