Adult T-Cell Leukemia: Clinical and Hematologic Features of 16 Cases

By Takashi Uchiyama, Junji Yodoi, Kimitaka Sagawa, Kiyoshi Takatsuki, and Haruto Uchino

Clinical and hematologic studies of 16 adult patients whose leukemic cells had T-cell markers are reported from Japan, where the incidence of various lymphoproliferative diseases differs considerably from that in Western countries. Leukemic cells were studied by cytotoxicity tests with specific antisera against human T (ATS) and B cells (ABS) in addition to the usual T- and B-cell markers (E rosette, EAC rosette, and surface immunoglobulins). Characteristics of the clinical and hematologic findings were as follows: (1) onset in adulthood; (2) subacute or chronic leukemia with rapidly progressive terminal course; (3) leukemic cells killed by ATS and forming E rosettes; (4) leukemic cells not morphologically monotonous and frequent cells with deeply indented or lobulated nuclei; (5) frequent skin involvement (9 patients); (6) common lymphadenopathy and hepatosplenomegaly; (7) no mediastinal mass; and, the most striking finding, (8) the clustering of the patients' birthplaces, namely, 13 patients born in Kyushu. The relationship between our cases and other subacute or chronic adult T-cell malignancies such as chronic lymphocytic leukemia of T-cell origin, prolymphocytic leukemia with T-cell properties, Sézary syndrome, and mycosis fungoides is discussed.

In man, as well as in other species, the lymphoid cells consist of two main populations, T and B cells, which differ in cell surface properties, function, and ontogeny. Characterization of human lymphoid neoplastic cells using cell surface markers of T and B cells has given us a better understanding of the origin and nature of the neoplastic cells and deeper insight into the pathogenesis of various lymphoproliferative diseases. Some new classifications of lymphoid neoplastic diseases based on cell surface marker analyses have been reported recently. B-cell malignancies are more common in adults than T-cell malignancies such as Sézary syndrome, mycosis fungoides, and acute lymphocytic leukemia of T-cell origin. Chronic lymphocytic leukemia of T-cell origin (T-CLL) is extremely rare, but several cases have been reported in Japan, where the incidence of lymphoproliferative disorders differs from that in Western countries and CLL is much less common. We have previously reported two cases of T-CLL and have subsequently encountered 14 more adult patients whose leukemic cells have T-cell properties. Characteristic clinical features, cytologic and immunologic findings of the leukemic cells, and the peculiar geographic distribution of the birthplaces of the patients have led us to consider this leukemia, which we have tentatively called "adult T-cell leukemia," to be a new type of T-cell malignancy which has an...
adult onset and is apparently closely related to the classical CLL of T-cell origin and the typical Sézary syndrome. The results of clinical and hematologic studies are presented here; details of the characterization of the leukemic cells will be described separately.  

MATERIALS AND METHODS

Patients

Three patients with lymphocytic leukemia were admitted to Kyoto University Hospital and referred to us for characterization of the leukemic cells. The other 13 patients were referred to our laboratory from other hospitals, mainly around Kyoto.

Cytochemistry

Peripheral blood and bone marrow smears were stained with May-Grünewald-Giemsa; periodic acid-Schiff (PAS) and acid phosphatase activity were examined by the usual cytochemical techniques.

Electron Microscopic Studies

For electron microscopy, cell pellets were fixed in 2%, glutaraldehyde, postfixed in 1% osmium tetroxide for 120 min, and embedded in Epon 812. Ultrasections were stained with lead citrate and uranyl acetate.

Cell Surface Marker Analysis of Leukemic Cells

Details of the characterization of leukemic cell membrane will be presented separately. In brief, lymphocytes or lymphoid cells were separated by Ficoll-sodium metrizoate gradient centrifugation or simply obtained after sedimentation of erythrocytes by gravity in cases with a high white blood cell count. Sheep red blood cell (E) rosette-forming cells were detected by a slight modification of the method described by Jonndal et al. C3 receptors were detected by use of erythrocytes (E) coated with rabbit anti-E IgM antibodies and complement (EAC rosettes) by the method of Nussenzweig et al. Surface immunoglobulins (S Ig) were studied by a direct immunofluorescence technique in ice with fluorescein isothiocyanate (FITC)-conjugated antisera for the Fab fragment of normal human IgG prepared in our laboratory or FITC-conjugated anti-human immunoglobulins (Behringwerke, Marburg Lahn, West Germany), which had been absorbed with human erythrocytes before staining.

Cytotoxicity tests with rabbit antisera against human thymocyte membrane antigens (ATS) and against CLL cells with B-cell properties (ABS) were also performed. The preparation and characterization of these antisera have been partially described and will be reported in detail elsewhere. Briefly, ATS was heat inactivated and absorbed with human erythrocytes, liver powder, insolubilized serum protein, and bone marrow cells. ABS obtained by intravenously injecting CLL cells having surface immunoglobulins and complement receptors was heat inactivated and absorbed with human erythrocytes, serum protein coupled on Sepharose 4B, and fresh thymocytes. Cytolytic effects of these antisera were examined by incubating lymphoid cells in the presence of appropriately diluted antisera and guinea pig complement in a microtiter plate. Viability of cells was determined by trypan blue dye exclusion. The values for normal peripheral blood lymphocytes in our laboratory were as follows: E rosette 32%, 79% (average 59%); ATS (percent killed) 35%, 64% (48%); S Ig 12%, 31% (24%); EAC rosette 7%, 26% (12%); ABS (percent killed) 25%, 53% (35%).

Studies

It is appropriate to present briefly four representative cases before summarizing the clinical and hematologic findings of our 16 cases because subacute or chronic T-cell leukemia in adulthood is relatively rare and the clinical features are not clearly delineated.

Patient 1. This patient was a 50-yr-old female who had been born in Okino-erabu-shima, a small island south of Kyushu. For 10 yr she had been troubled with left hemiparesis. At the age
of 47, lymphocytosis of about $4.0 \times 10^9$ liter was first noticed. Pea-sized left axillary and left inguinal lymph nodes were felt, while splenomegaly, hepatomegaly, and skin lesions were not detected. Leukemic lymphocytes were morphologically monotonous, normal-appearing small lymphocytes. Without any treatment, she has been well for 6 yr.

**Patient 4.** A 62-yr-old female, this patient had been born in Makurazaki, a seaside town in Kagoshima prefecture in Kyushu. She noted cervical lymph node enlargement in December 1974. Physical examination at admission revealed marked generalized lymph node enlargement and hepatosplenomegaly. The leukocyte count in the peripheral blood was $28.0 \times 10^9$ liter, with $92\%$ lymphocytes. Large atypical lymphoid cells with lobulated or indented nuclei were occasionally seen (Fig. 1A). She was treated with cyclophosphamide and corticosteroid without remarkable improvement. Skin lesions due to the infiltration of leukemic cells then appeared on the neck and upper part of the chest. She died 4 mo after admission. Autopsy showed that the lungs, lymph nodes, liver, spleen, and bone marrow had been affected.

**Patient 5.** The patient, a 47-yr-old female, had been born in Fukuoka prefecture in Kyushu. She was admitted because of shortness of breath and icterus. Hepatosplenomegaly was noted but superficial lymph nodes were not enlarged. Neither anemia nor thrombocytopenia was present. Leukemic cells in the peripheral blood and bone marrow were not monotonous. Relatively large cells with deeply indented or lobulated nuclei were observed. Histologic examination of specimens obtained from a coin-sized lesion on the right knee revealed infiltration of leukemic cells into the dermis and subcutaneous tissue. Blood chemistries showed high levels of serum transaminases,
bilirubin, and alkaline phosphatase. Corticosteroid and vincristine therapy was not effective. Postmortem examination revealed that lymph nodes, spleen, liver, and bone marrow had been infiltrated with leukemic cells.

Patient 9. This patient was a 61-yr-old male who had been born in northern Kyushu. He noted eruptions on the lower extremities 7 mo before admission. On admission generalized exfoliative erythroderma with itching, generalized superficial lymph node enlargement, hepatosplenomegaly, and high white blood cell count (193.0 × 10^9/liter) were detected. Some of the leukemic cells in the peripheral blood on May Giemsa stained smears closely resembled Sézary

![Electron micrograph of leukemic T cells. (A) Nucleus of a leukemic cell from patient 1 is not deeply indented. ×10,000. (B) In patient 9, nucleus is deeply indented but not so markedly convoluted or serpentine as that of the typical Sézary cell. ×6480.](image-url)
Table 1. Clinical and Hematologic Findings in Patients With "Adult T-Cell Leukemia"

<table>
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<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Survival (mo)</th>
<th>Lymphadenopathy</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Skin Lesion</th>
<th>Bone Marrow (Percent lymphocytes)</th>
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Abbreviations: F, female, M, male, - absent, + slight, ++ moderate, +++ massive enlargement.
microabscesses seen in Sézary syndrome and mycosis fungoides was not found. No mediastinal mass was shown roentgenologically and neither thymoma nor thymic involvement was demonstrated histologically in 8 autopsied cases.

Chest x-ray revealed abnormal shadows in the lung fields in 4 cases, probably due to the infiltration of leukemic cells. Serum immunoglobulin levels were almost normal in “adult T-cell leukemia” in contrast with hypogammaglobulinemia in B-CLL as shown in Fig. 3. Neither autoantibodies nor M protein was found in adult T-cell leukemia. Serum IgE levels determined by radioimmunoassay were also normal in the four cases examined.

Hematologic Findings

Mild anemia was seen in 4 patients at the time of diagnosis. A high white blood cell count (more than 100.0 × 10⁹/liter) was found in 9 cases. In another 7 cases the leukocyte count was between 27.0 and 85.0 × 10⁹/liter. The percentage of lymphoid cells in the bone marrow was less than 30%, of all nucleated cells in 5 patients, 30%–60% in 5 patients, and more than 60%, in 5 patients. In May Giemsa stained smears, leukemic cells were not morphologically monotonous, but showed pleomorphism in all but patients 1 and 7. Leukemic cells of slightly larger size than red blood cells (9.15 μm) with indented or lobulated nuclei, relatively coarsely clumped nuclear chromatin, and scant cytoplasm were predominant. Small, fairly normal appearing, mature lymphocytes and larger atypical lymphocytes with some resemblance to typical Sézary cells were also occasionally found. Nucleoli were occasionally found in larger leukemic cells. In patients 1 and 7, leukemic cells were fairly uniform in size and almost all cells were small, normal-appearing mature cells usually seen in classical CLL. Leukemic cells appeared fragile and nuclear ghosts were frequently seen in smears of peripheral blood from 7 patients.

Cytochemical studies were performed in a limited number of patients. PAS-positive granules were demonstrated in 2 of 4 cases examined and acid phosphatase was positive in 2 of 3 cases. Electron microscopic studies of leukemic cells in the peripheral blood were done in 6 cases. In patient 1, electron microscopic features of leukemic T cells were those of classical lymphocytic leukemia cells and nuclei were not deeply indented as shown in Fig. 2A. In other cases leukemic cells with deeply indented or lobulated nuclei were fre-
Table 2. Cell Surface Markers of Leukemic Cells From Patients With Diseases Other Than "Adult T-Cell Leukemia": Reactivity of ATS and ABS Against Leukemic Cells

<table>
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<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>WBC (x 10^9/liter)</th>
<th>Leukemic Cells (%)</th>
<th>E Rosettes (%)</th>
<th>ATS (Percent Killed)</th>
<th>Sig (%)</th>
<th>EAC Rosettes (%)</th>
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Abbreviations: M, male; F, female; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; SS, Sézary syndrome; LLSC, leukaemic lymphosarcoma; HD, Hodgkin disease; PCL, plasma cell leukemia; AML, acute myelocytic leukemia; MoL, monocytic leukemia; CCRF-CEM, established T-cell line from Flow Laboratory, Rockville, Md.

Recently found as shown in Fig. 2B. However, the markedly convoluted or serpentine nuclei which have been reported to be among the most important characteristics of typical Sézary cells were not found.

Specificity of ATS and ABS

The specificities of ATS and ABS were evaluated by their cytotoxic effect on various kinds of cells in the presence of complement and by their inhibitory effect on E and EAC rosette formation. The results of the cytotoxicity tests against various leukemic cells other than adult T-cell leukemia cells are summarized in Table 2. At up to 1/100 dilution, ATS killed 95%, of thymocytes, 35%, 64%, of normal peripheral blood lymphocytes, and less than 10%, of CLL

Table 3. Cell Surface Markers of Leukemic Cells From Patients With "Adult T-Cell Leukemia"

<table>
<thead>
<tr>
<th>Patient</th>
<th>WBC (x 10^9/liter)</th>
<th>Lymphoid Cells (%)</th>
<th>E Rosettes (%)</th>
<th>ATS (Percent Killed)</th>
<th>Sig (%)</th>
<th>EAC Rosettes (%)</th>
<th>ABS (Percent Killed)</th>
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cells bearing surface immunoglobulins and complement receptors (B-CLL cells). ATS without complement almost completely inhibited E but not EAC rosette formation. At up to 1/50 dilution, ABS killed 60\%, 80\% of B-CLL cells, 25\%-53\% of normal peripheral blood lymphocytes, less than 7\% of cells from a patient with Sézary syndrome, and less than 10\% of thymocytes. ABS partially inhibited EAC but not E rosette formation.

**Cell Surface Markers of Leukemic Cells**

Results of cell surface marker analyses are summarized in Table 3. Leukemic cells formed nonimmune rosettes with sheep red blood cells and were killed by ATS, whereas they had neither surface immunoglobulins nor complement receptors. In patient 8, the leukemic cells did not form E rosettes with three different lots of sheep erythrocytes, but were killed by ATS. The cells, however, had been reported to form E rosettes in high proportion on examination in another laboratory 2 mo previously. Leukemic cells from 8 of 12 patients were killed by ABS. This reactivity will be discussed later.

**Geographic Pathology**

Birth and dwelling places of patients with this leukemia are shown in Fig. 4. Japan consists of four major islands, Hokkaido, Honshu, Shikoku, and Kyushu. The patients lived in or around big cities in Honshu, including Kyoto, Osaka, and Kobe, but, curiously, 13 of the 16 patients were born in Kyushu, 8 of them in Kagoshima prefecture, and had grown up in their native places before moving. While many natives of Kyushu migrate to the big cities of Japan.
Honshu, the marked predominance of Kyushu natives among patients with adult T-cell leukemia was not found among patients with other lymphoproliferative diseases studied in our laboratory in the same period. For example, the birthplaces of 6 of 11 cases of B-CLL were known, and of these only one was Kyushu.

**Treatment and Clinical Course**

Most patients have been treated with adrenal corticosteroids and other anti-tumor agents such as cyclophosphamide, vinca alkaloids, 6-mercaptopurine, procarbazine, and 5-fluorouracil with partial and temporary improvement of the disease before the final rapidly progressive course. Patient 1 has been well for more than 6 yr and requires no therapy. Two other patients are still alive. Survival time from onset of the disease has ranged from 3 mo to more than 6 yr. In the course of the disease the severe infections frequently encountered in B-CLL rarely have been seen.

**DISCUSSION**

In the present study we have presented a new type of adult-onset T-cell leukemia with the following characteristics: (1) onset in adulthood; (2) leukemic cells with T-cell properties; (3) leukemic cells with morphologically characteristic features: (4) lymphadenopathy and hepatosplenomegaly; (5) no mediastinal masses, (6) subacute or chronic course; and (7) predominance among natives of Kyushu.

The types of adult subacute or chronic leukemia in which leukemic cells have been shown to have T-cell surface markers are Sézary syndrome, rare cases of CLL, and a minority of cases of its variant, prolymphocytic leukemia. Lutzner and colleagues have studied neoplastic cells from patients with Sézary syndrome, mycosis fungoides, and related diseases and have suggested that these lymphoproliferative disorders be grouped together as “cutaneous T-cell lymphoma.” Our cases of “adult T-cell leukemia” are different from classical Sézary syndrome due to: (1) the absence of typical Sézary cells; (2) the absence of infiltration of leukemic cells into the epidermis, despite their infiltration into the dermis or subcutaneous tissue in all 7 patients with skin involvement; (3) the infiltration of leukemic cells into bone marrow; and (4) the shorter survival time. Our cases of adult T-cell leukemia without skin infiltration may be distinguished from cutaneous T-cell lymphoma, but those with skin involvement are similar to the small-cell variant of Sézary syndrome and are difficult to differentiate.

The clinical features of T-CLL have not been clearly delineated because of its rarity. Brouet et al. reported 11 patients with T-CLL and documented its characteristic clinical and hematologic features usually absent in classical CLL: massive splenomegaly, only moderate bone marrow infiltration, a high content of lysosomal enzymes and cytoplasmic granules in the leukemic cells, and increased frequency of skin lesions and severe neutropenia. Our cases, with the exception of patient 1, were also different from classical CLL in the following findings: (1) morphologic findings of leukemic cells (not monotonous and fre-
quent cells with indented or lobulated nuclei; (2) clinical course (rather shorter);
(3) mode of infiltration of leukemic cells (frequent skin involvement and slight
bone marrow infiltration in several cases); and (4) serum immunoglobulin levels
(almost normal). Clinical and hematologic features of our cases were similar to
those of Brouet's series, but differed in that (1) numerous cytoplasmic granules
were not found in leukemic cells, (2) hepatomegaly and peripheral lymph node
enlargement were more common, and (3) patients' birthplaces showed a unique
geographic distribution.

Galton and associates have described prolymphocytic leukemia, a rare
variant of CLL, and reported that leukemic cells were in most cases of B-cell
origin but in some rare cases of T-cell origin. Two of 11 patients reported
by Brouet et al. and patients 2, 5, and 14 of our series seemed to have clinical
and hematologic features of prolymphocytic leukemia, but others did not.

Thus, although the clinical and hematologic features of adult T-cell leukemia
closely resembled, or in some cases were related to, those of T-CLL, pro-
lymphocytic leukemia with T-cell properties, and the small-cell variant of Sézary syndrome, the peculiar characteristics mentioned above suggest
strongly that this leukemia is a new type of T-cell leukemia. To ascertain
whether these T-cell malignancies reported from different places are the same
disease, further comparative studies will be necessary. It is possible that the
unique features observed in our adult T-cell leukemia cases may be due to racial
differences or genetic factors. It is well known that the incidence of hematologic
malignancies in Japan differs somewhat from that in Western countries. For
example, of the 2323 cases of hematologic neoplasms registered in Japan from
1972 to 1973 by the Joint Committee for Hematological Neoplasms, only 22
(1.0%) were CLL, although the incidence of multiple myeloma (6.3%), ne6-
plasms of terminally differentiated B cells, was not as low as in Europe and
America.

As to the significant reactivity of leukemic cells from 8 patients with ABS,
it has not yet been determined what factors (antibodies) contained in ABS were
responsible. The reactivity may have been due to "CLL" antigen(s) on leukemic
T cells, because ABS was prepared against B-CLL cells and ABS did not kill
thymocytes, neoplastic T cells other than adult T-cell leukemia cells, cell line
cells with T-cell properties, lymphoid neoplastic cells without T- and B-cell
markers, and myeloid or monocytic leukemia cells.

Leukemic cells in adult T-cell leukemia appear to have their origin in fairly
well-differentiated T cells, because (1) this leukemia affects adults; (2) no
mediastinal mass (thymoma), as often seen in childhood acute lymphoblastic
leukemia with T-cell properties, is found, and leukemic cells have no affinity
for the thymus and are not under thymic influence; (3) leukemic cells show
macrophage migration inhibitory factor-like activity, and in some cases they
show a suppressive effect on pokeweed mitogen-induced B-cell differentiation
into immunoglobulin-producing cells, and (4) proliferation of the leukemic
cells is poor in vitro and it is very difficult to establish T-cell lines derived from
patients with this leukemia. A comparative study of the antigenicities of leu-
kemic cells with those of thymocytes, normal peripheral T lymphocytes, and
leukemic T cells in childhood acute lymphoblastic leukemia is now in progress
and will provide some indication as to the origin and the nature of the neoplastic cells in this leukemia.

Our observation of the peculiar geographic distribution of the patients' birthplaces has been supported by recent reports from other laboratories in our country. This finding should not be overlooked in considering the pathogenesis and etiology of this leukemia. Genetic background may play an important role but other factors such as oncogenic virus infections must be explored.

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