J Korean Med Sci 2000; 15: 233-9
ISSN 1011-8934

Adult T Cell Leukemia/Lymphoma with Lymphopenia in a Korean

We experienced a case of adult T cell leukemia/lymphoma (ATLL) in a 48-year-old Korean female, who has never been abroad since birth and no history of blood transfusion. The patient had hypercalcemia and multiple lymphadenopathy. Histopathologic study of left cervical lymph node (LN) and bone marrow (BM) revealed that infiltrates of malignant lymphoid cells were composed of small, medium and large cells with pleomorphic nuclei. Smears of peripheral blood (PB) showed lymphopenia (16%) with the appearance of a few atypical lymphoid cells (less than 2%), but not the typical clover leaf cells seen in ATLL. Immunophenotypic study of LN and BM revealed T cell phenotype. PB showed increased CD4+ T cell (T_H, CD3/CD4+, 57%) and decreased CD8+ T cell counts (T_S, CD3/CD8+, 6.7%). The sera of the patient and her family were reactive for HTLV-I antibody. The specific sequences of *pol, env,* and *tax* of HTLV-I DNA were detected in the lymphoma cells and peripheral blood mononuclear cells (PBMC) using polymerase chain reaction. Ultrastructural examination of PBMC confirmed numerous type c virus particles in extracellular space. This case was an acute type of ATLL without overt leukemic features in PB. Despite chemotherapy and intensive conservative treatment, she died 3 months after admission.

Key Words: *Leukemia/Lymphoma, Adult T Cell; HTLV-I; Polymerase Chain Reaction; Flow Cytometry; Hypercalcemia*

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Received: 8 August 1999
Accepted: 13 September 1999

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*This article was presented at the 50th annual meeting of the Korean Society of Pathologists held on October 30 & 31, 1998 at Asan Medical Center, University of Ulsan Medical School, Korea. This study was supported by research funds from Chosun University, Korea, 1998.

INTRODUCTION

Since a series of ATLL patients was reported in 1977 (1), many cases of ATLL have been confirmed in Japan, particularly in the Kyushu area. In addition, HTLV-I was demonstrated to be an etiologic agent for ATLL (2, 3). HTLV-I is endemic to southern Japan (4), the Caribbean area (5), and Central Africa (6). But ATLL associated with HTLV-I has rarely occurred in Korea, at present only four cases of ATLL have been reported in Korea (7-10).

ATLL can be broadly classified as an asymptomatic carrier state, a preleukemic state (pre-ATLL), chronic, smouldering, acute, and lymphoma type according to clinical features and course of disease (11-13). ATLL manifestations vary in clinical features, complications, and prognosis, suggesting the need for diverse therapeutic regimens as therapy (12). In smouldering and chronic cases, chemotherapy is not recommended. However, aggressive chemotherapy is necessary in acute cases, even though the acute type shows extremely poor prognosis despite aggressive treatment. It is now known that the vast majority of HTLV-I infected individuals are healthy carriers, who do not manifest any overt signs or symptoms of ATLL (14). In epidemiologic studies, Lee et al. (15) reported 0.25% positivity of serum antibodies against HTLV-I without evidence of ATLL and Kim et al. (16) revealed 0.16% positivity of serum anti-HTLV-I in blood donors in Korea.

ATLL diagnosis is based on clinico- and histopathological findings and the presence of integrated HTLV-I provirus in the DNA of tumor cells (17). T-cell lymphoma with clonal integration of HTLV-I and anti-ATLL antigen has been considered to be ATLL (lymphoma type) (18). The histopathology of lymphoma usually indicates a pleomorphic type.

We experienced a case of Korean ATLL (acute type) that showed anti-HTLV-I antibody in serum and clonal integration of HTLV-I proviral DNA in both PBMC and neoplastic cells of nodal lymphoma, with hypercalcemia, multiple lymphadenopathy, BM infiltration, lymphopenia, elevation of serum LDH, PTH related peptide, and the absence of skin lesion, hepatosplenomegaly, and overt leukemic features in PB.

CASE REPORT

A 48-year-old Korean female patient visited a local clinic due to back pain. Three weeks later she was referred to the Chosun University Hospital in May 1998 because of nausea, vomiting and generalized malaise. She was born in Korea and had no history of travel abroad and blood transfusion. Multiple lymph nodes were palpated in left neck. An abdominal spiral CT showed multiple lymphadenopathy in retroperitoneum (Fig. 1), but not hepatosplenomegaly. Laboratory data revealed WBC of 8,500/μL with lymphopenia (16%), Hb of 8.5 g/dL, and platelet count of 224,000/μL. The serum SGOT/ SGPT level was 61/97 U/L, calcium level, 15.5 mg/dL (reference range: 8.5-11.0 mg/dL), lactate dehydrogenase (LDH) level, 989 IU/L (reference range: 218-472 IU/L), Na^+ level, 151 mEq/L (reference range: 136-142 mEq/L), BUN/Cr level, 100/2.3 mg/dL (reference range: 8-23/0.6-1.2 mg/dL), and parathyroid hormone (PTH) related peptide (PTHrP) level, 485.9 pmol/L (reference range: 13.8-55.3 pmol/L). Atypical lymphoid cells with indented nuclei, but not typical "clover-leaf", were seen about less than 2% on PB smear. BM biopsy showed interstitial infiltration of malignant lymphoid cells, which were intermingled with normal hematopoietic cells. The malignant lymphoid cells revealed an abnormal population of pleomorphic lymphocytes varying in size from large to small, some of them showed convoluted nuclear pattern with two or three prominent nucleoli (Fig. 2). Histopathologic examination of a left cervical LN revealed infiltration of various-sized neoplastic cells compatible with pleomorphic type lymphoma (Fig. 3). The tumor cells showed pleomorphic small, medium, and large cells. The large cells were irregularly shaped with convoluted and multilobulated forms ("jellyfish" appearance) (Fig. 4), having two or three small nucleoli. Mitoses were frequently seen. The immunophenotype of malignant cells

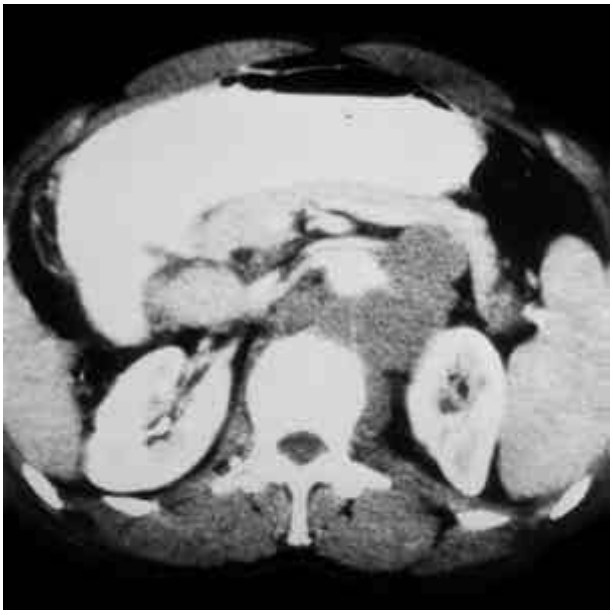

Fig. 1. Abdominal spiral CT shows multiple lymphadenopathy in retroperitoneum.

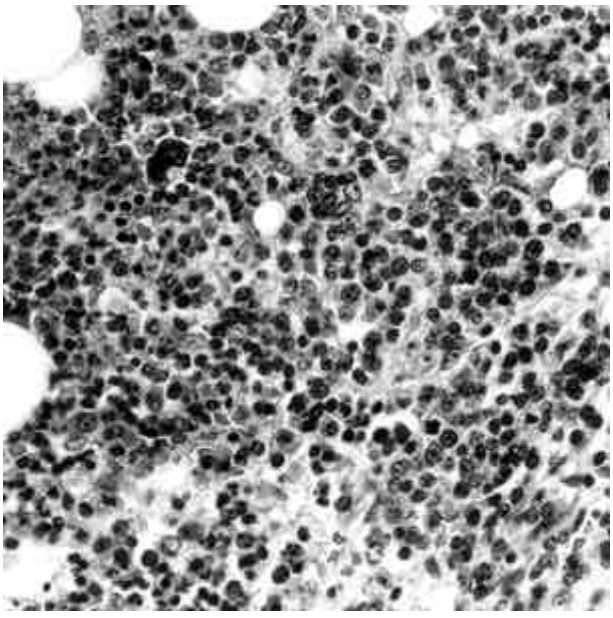

Fig. 2. Bone marrow shows diffuse infiltration of neoplastic cell with pleomorphism (H&E, ×200).

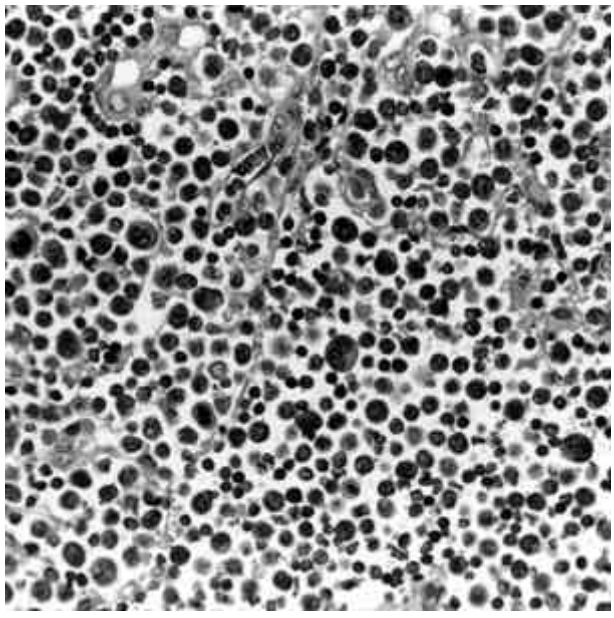

Fig. 3. The cervical lymph node biopsy reveals infiltration of various-sized neoplastic cells compatible with pleomorphic type of lymphoma. The tumor cells show pleomorphic small, medium, and large cells (H&E, ×200).

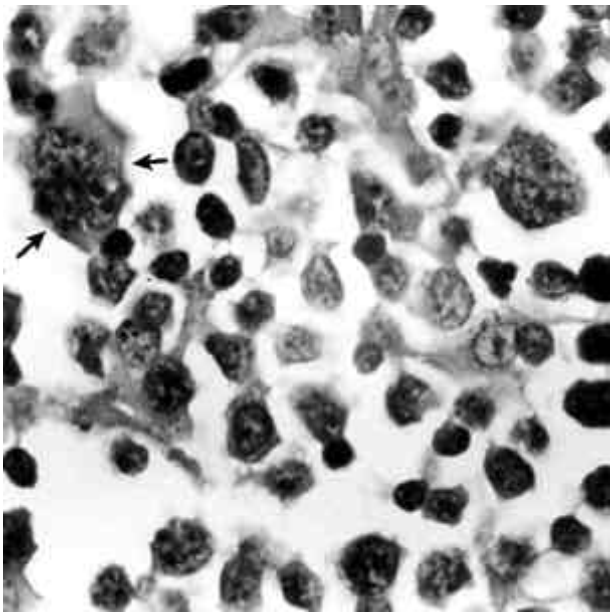

Fig. 4. The large cells are markedly irregular in shape with convoluted and multilobated forms ("jellyfish" appearance, arrow) (H&E, ×400).

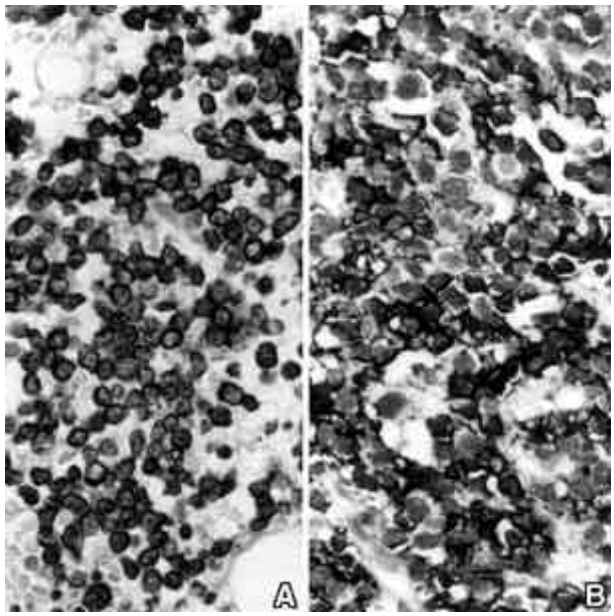

Fig. 5. Immunohistochemical stainings of bone marrow (B) and lymph node biopsy (A) are reactive for CD3 (ABC, ×200).

in BM and LN were T cell by immunohistochemical stain (LCA+, UCHL-1+, CD3+) (Fig. 5), but were nonreactive to B cell marker (CD20). Immunophenotyping of PB lymphocytes by flow cytometry (Table 1) showed lymphopenia, which revealed increased CD4+ T cell (CD3/CD4+, 57%) and decreased CD8+ T cell counts (CD3/CD8+, 6.7%). The ratio of CD4+/CD8+ T cells was 8.5:1 (Fig. 6). The serum of patient showed reactivity to HTLV-I antibody. The presence of HTLV-I proviral genome was confirmed by PCR. The specific *pol, env,* and *tax* sequences of HTLV-I showed amplified fragments of 186, 271 and 159 base pairs, respectively, in the extracted DNA from lymphoma and PBMC with positive control by DNA from the ATL-1T cell line (19). *Tax* sequence is not amplified in positive control (Fig. 7). Ultrastructural examination (Fig. 8) of PBMC of patient disclosed numerous type c virus particles in extracellular space.

Table 1. Immunophenotyping of peripheral blood lymphocytes by flow cytometry

Antibody	Results (%)
CD3	54.2
CD3/CD4	57.0
CD3/CD8	6.7
CD5	28.7
CD7	18.6
CD19	13.8
CD20	7.2
CD22	10.6
CD10	0
HLA-DR	15.0
CD16+56	10.3
CD14	1.4
CD13	0*
CD33	0*

*only lymphocytes were gated and counted

She had herpes zoster skin lesions and post therapeutic neuralgia in left back and left leg. She was treated once with chemotherapy accompanied with cyclophosphamide, adriamycin, vincristine, and prednisone. She died 3 months later after admission because of cardiac arrhythmia due to hypercalcemia. Autopsy was not performed.

According to the family history, the sera of the husband, a 24-year-old son and a 21-year-old daughter showed antibody for HTLV-I.

DISCUSSION

HTLV-I is the causative agent in both a hematopoietic malignancy, ATLL, and progressive myelopathy called tropical spastic paraparesis/HTLV-I associated myelopathy (HAM) (20-21). The discovery of HTLV-I was followed a few years later by the discovery of HTLV-II (22) and the rapid identification of human immunodeficiency virus (HIV) (23). HTLV-II has been isolated from a variant form of hairy T-cell leukemia and from other hematologic patients (24). HTLV-I is transmitted through breast milk, sexual contact, and blood products (25).

ATLL is a mature T-cell leukemia/lymphoma, most

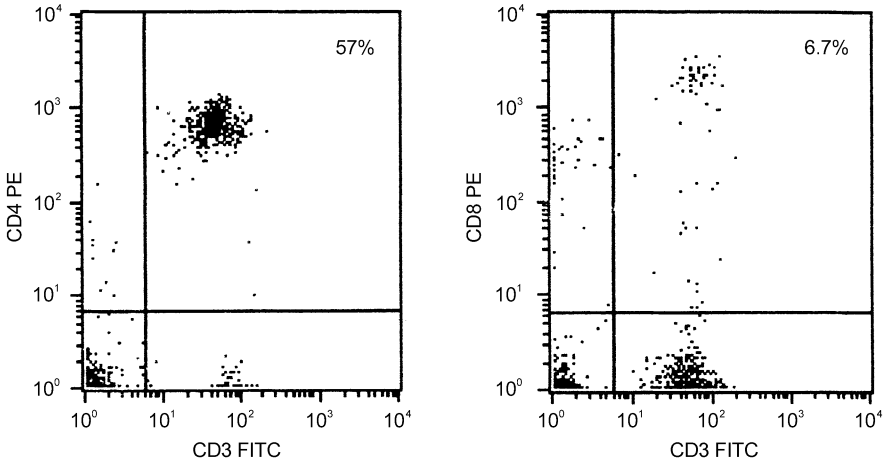

Fig. 6. Immunophenotyping of peripheral lymphocytes by flow cytometry shows lymphopenia with increased helper T cell (CD3/CD4+, 57%) and decreased suppressor T cell (CD3/CD8+, 6.7%). The ratio of T_H/T_S is 8.5:1.

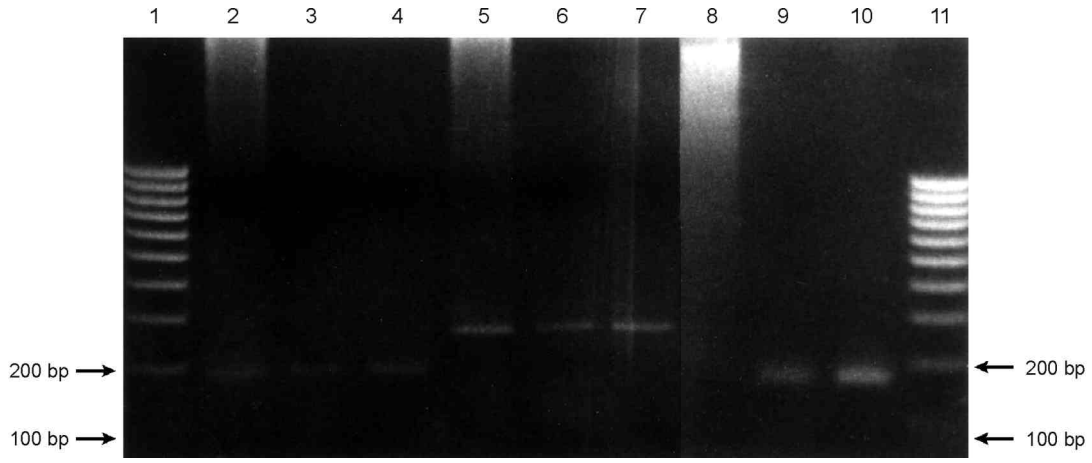

Fig. 7. PCR amplification analysis for HTLV-I DNA primers, *pol*, *env*, and *tax* in peripheral blood mononuclear cells (PBMC) and lymphoma, with positive control by DNA from the ATL-1T cell line. The specific *pol*, *env*, and *tax* primers of HTLV-I shows amplified fragments of 186, 271, 159 base pair respectively in the lymphoma and PBMC. Lane 1, 11: molecular marker (100 bp ladder); lane 2, 5, 8: positive control (ATL-1T) in *pol*, *env*, *tax* respectively; lane 3: *pol* primer in lymphoma; lane 4: *pol* primer in PBMC; lane 6: *env* primer in lymphoma; lane 7: *env* primer in PBMC; lane 9: *tax* primer in lymphoma; lane 10: *tax* primer in PBMC.

often of CD4+/CD8− phenotype, that occurs in very small numbers (2% to 5%) of HTLV-I infected people within their lifetime (25). The estimated average time between HTLV-I infection and occurrence of malignancies is 20 to 30 years (26). Epidemiologic data indicates that ATLL develops mainly in individuals infected at birth. These results suggest that the age at the time of viral infection may be an important factor in the onset of leukemia (25).

Clinically, ATLL is a rapidly aggressive and lethal disease (with mean survival of 6 months). ATLL often presents the symptoms of hypercalcemia, skin infiltration, hepatosplenomegaly, lytic bone lesions, and bone marrow involvement (25). The pathognomic feature in ATLL is the presence of large flower-like cells with lobulated nuclei in the peripheral blood (11).

The clinical course of ATLL comprises at least four different subtypes, i.e., acute, chronic, smouldering, and lymphomatous, depending on the extent of disease and the serum calcium level (11, 12). Acute type was the so-called prototypic ATLL. Features of acute ATLL include leukocytosis, in which the abnormal lymphocytes have characteristic lobulated or flower-shaped nuclei; mild to moderate lymphadenopathy; hepatosplenomegaly; skin lesions, due to leukemic infiltration; lytic bone lesions; and serum LDH elevation, bilirubin, and calcium. Most patients in this group are resistant to chemotherapy and die rapidly.

Chronic type ATLL was defined as a manifesting chronic course with more frequent ATLL cells in the PB (more than 10%) than in smouldering type. The patients suffered mainly from increased leukocyte count (more

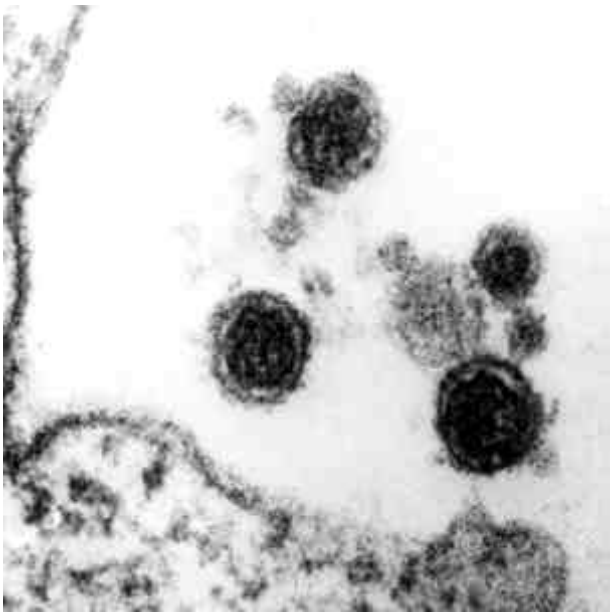

Fig. 8. Ultrastructural findings of PBMCs from patient show numerous type c virus particles in the extracellular space.

than 10,000/μL), cough and skin disease. Slight lymphadenopathy and hepatomegaly were observed in a few chronic-type patients. An elevation in serum LDH was also noted in a few patients, but this was not associated with hypercalcemia or hyperbilirubinemia. Smouldering ATLL is characterized by long duration of a few ATLL cells (0.5-3%) in the PB. Patients with smouldering type frequently have skin lesions such as erythema, papules, or nodules. The serum LDH value was within normal range and was not associated with hypercalcemia, lymphadenopathy, or hepatosplenomegaly, and bone infiltration was very slight. Smouldering ATLL often progressed to typical ATLL after a long duration. It is necessary to distinguish between the course of smouldering ATLL and those of other non-ATLL T-cell malignancies, including symptoms such as skin lesions. In Sezary syndrome and mycosis fungoides, infiltration of tumor cells is extensive; in smouldering ATLL, it is slight. Furthermore, in typical cases of Sezary syndrome and mycosis fungoides, the HTLV-I antibody in serum is negative. In ATLL patient, proviral DNA is confirmed in 100% of the cases. All of these ATLL pateints were also positive for HTLV-I antibody. Some ATLL patients have been described in lymphoma type which presents predominantly as a T-cell lymphoma rather than a leukemia (27). These non-Hodgkin's lymphomas vary in histology, and can involve any organ. LN biopsy specimens from these ATLL patients contain oligoclonally integrated HTLV-I as determined by Southern blot hybridization (17, 18). Distinguishing patients with lymphoma type ATLL from those with non-HTLV-I related T cell lymphoma is important, since the prognosis and therapeutic response of ATLL are different from that of other T cell lymphomas. The differential diagnosis of ATLL includes other T cell malignancies such as non-Hodgkin's lymphoma, mycosis fungoides, Sezary syndrome, and T cell chronic lymphocytic leukemia (CLL). A variety of laboratory studies can help establish the diagnosis of ATLL. These include a positive HTLV-I serology; elevated serum calcium and LDH; staining for terminal deoxynucleotidyl transterase (TdT), which is typically negative in ATLL; and immunologic phenotyping of ATLL cells, which characteristically express both the CD4 and anti-Tac (interleukin 2 receptor, IL-2R) antigens. However, the presence of monoclonally or oligoclonally integrated HTLV-I in the malignant T cell clone is definitive evidence of the disease.

Our case was compatible with the acute type of ATLL, presenting with hypercalcemia, elevation of serum LDH, hypernatremia, PTHrP, increased BUN/Cr, multiple lymphadenopathy, BM infiltration, and typical clinical course of acute ATLL, i.e., the disease progressed rapidly and became refractory to chemotherapy to fatal termination. And this patient showed nodal T cell lymphoma, pleomorphic type, anti-HTLV-I antibody in serum, clonal integration of HTLV-I proviral DNA in both PBMC and neoplastic cells of nodal lymphoma, and confirmation of type c virus particles in PBMC. Since this patient did not show skin lesions, hepatosplenomegaly, or overt leukemic features on PB smears (less than 2% of atypical lymphoid cells) and revealed lymphopenia (16%), this case was a little different from those commonly seen in acute type of ATLL. Further studies will be necessary to clarify increased helper T cell (CD3/CD4+, 57%) and the ratio of T_H/T_S (8.5:1) of peripheral blood lymphocytes, although a few atypical lymphoid cells were seen on PB smear.

Identification of HTLV-I infected individuals is of both practical and academic importance. Knowledge of HTLV-I sero-positivity may help in preventing transmission between sexual partners, as well as transmission from mother to child. It may also assist in establishing a diagnosis of ATLL or HAM. HTLV-I has been rarely involved in Koreans, but on epidemiologic studies. Lee et al. (15) reported 0.25% positivity of serum antibodies of HTLV-I without evidence of ATLL, and Kim et al. (16) revealed 0.16% positive rate of serum anti-HTLV-I antibody in blood donors in Korea. Also, four cases of ATLL (7-10) (Table 2) and one case of HAM (28) have been reported with all HTLV-I antibody in Korea. As transmission can occur by transfusion, a blood screening test for HTLV-I should be initiated in Korea. In our case, the patient had never been abroad since birth and no history of blood transfusion. According to the family history, the husband, a son and a daughter were reactive for HTLV-I antibody.

Table 2. Reported and present cases of adult T cell leukemia/lymphoma in Korea

Case	Ref	Age/Sex	History	Skin	LAP	HS	Leuk*	PB	BM	Ca	LDH	Ab	Lymp	PCR	Western	Subtype	Follow up
1	7	28/M	Mother: HTLV-I carrier transfusion+	+	+	−	++	90%	+	−	+	+	+ (neck)	ND	ND	acute	expired (47 days)
2	8	44/M	-	+	+	+	++	87%	+	+	+	+	+ (neck)	pX+	*env* gp46+	acute	expired (21 days)
3	9	51/M	-	+	+	−	+	30%	+	−	+	+	+ (neck)	pX+ *gag, pol, env*+	core protein+ *env* gp46+	acute	refractory to chemotherapy
4	10	58/M	trip to Japan	+	−	−	+	-	−	−	+	+	+ (skin, testis)	pX+	ND	lymphoma	partial remission after chemotherapy
5	Present	48/F	husband and children: HTLV-I carrier	−	+	−	−	2%	+	+	−	+	+ (neck)	*pol, env, tax*+	ND	acute	expired (3 months)

*−, <10,000/μL; +, 10,000-50,000; ++, >50,000

Ref, references; Skin, skin lesion; LAP, lymphadenopathy; HS, hepatosplenomegaly; Leuk, leukocytosis; PB, atypical lymphocytes (%) on peripheral blood; BM, bone marrow infiltration; Ca, hypercalcemia; LDH, elevation of lactic dehydrogenase; Ab, HTLV-1 antibody in serum; Lymp, lymphoma; ND, not done; chemoTx, chemotherapy; −, absent; +, present

But the route of HTLV-I infection in this family was not clear.

The HTLV-I genome have *gag* (viral structural gene; nuclear core of the virus), *pol* (reverse transcriptase), *env* (viral envelope gene), unique pX (virus replication and transformation), and long terminal repeat (LTR) (11). HTLV-I has two *trans*-acting regulator genes, *tax* and *rex*, in the pX region. The *tax* gene is a *trans*-acting transcriptional activator of the LTR and also of the cellular gene for IL2R. The latter seems to explain the initiation of abnormal growth of HTLV-I infected cells. The *rex* gene for "regulator of expression" is a posttranscriptional regulator. Ohshima et al. (29) reported a series of 95 patients with ATLL in which 28 patients (29%) showed a defective HTLV-I provirus form of *env* and/or *gag* deletion, but the pX region was not deleted in any. Therefore, the pX region, which included the *tax* and *rex* genes, might have a close relationship to neoplastic changes. For this reason, HTLV-I proviral pX is the most reliable target in the detection of HTLV-I for screening purposes. In our case, HTLV-I proviral DNA, *pol*, *env*, and *tax* were detected in the neoplatic cells of lymphoma and PBMC by PCR.

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