Adult T-cell Leukemia/Lymphoma with Features of CD30-Positive Anaplastic Large Cell Lymphoma

- A Case Report -

We experienced a 58-year-old Korean man with adult T-cell leukemia/lymphoma with features of histologically anaplastic large cell lymphoma involving the skin and testis. The patient had cutaneous nodules in both extremities and a palpable right testicular mass. Right orchiectomy was performed and specimens of removed testicle and skin nodules showed immunohistologically anaplastic large cell lymphoma with T-cell phenotype, and CD30 antigen was positive. A human T-cell lymphotropic virus type 1 (HTLV-1) antibody titer was over 1 : 256 and integration of HTLV-1 proviral DNA *pX* gene was identified in the peripheral blood mononuclear cells and lymphoma tissue by polymerase chain reaction. Peripheral blood and bone marrow did not show any evidence of characteristic neoplastic T-cells. ***(JKMS 1997; 12 : 364~8)***

Key Words : *Adult T-cell leukemia/lymphoma, Anaplastic large cell lymphoma (Ki-1 lymphoma), Human T-cell lymphotropic virus type 1(HTLV-1)*

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INTRODUCTION

CD30 (Ki-1) antigen was initially recognized in a cell line derived from a patient with Hodgkin's disease (1) and subsequently expressed in some large cell lymphoma (2). Induction of CD30 expression by human T-cell lymphotropic virus type-1(HTLV-1) was initially reported in the peripheral blood lymphocytes *in vitro*(2).

HTLV-1 is integrated to adult T-cell leukemia/lymphoma (ATL/L), which was first reported by Uchiyama et al. (3) in Japan. Since then several typical clinical entities have been reported, and its viral etiology was very attractive for leukemia and lymphoma. Recently, some reports showed CD30 expression in ATL/L which was histologically anaplastic large cell type or diffuse pleomorphic type lymphoma (4~6). Otherwise, Anagnostopoulos et al. (7) reported six cases of CD30-positive large cell cutaneous T-cell lymphoma associated with HTLV-1 DNA in a nonendemic region and some studies of anaplastic large cell lymphoma (ALCL) (8, 9) showed monoclonal integration of HTLV-1 provirus which was detected by using polymerase chain reaction (PCR) or Southern blot hybridization method.

HTLV-1 has been rarely involved in the Korean patients with leukemia and lymphoma. We encountered a Korean patient with adult T-cell leukemia/lymphoma with histologically CD30-positive anaplastic large cell lymphoma that showed clonal integration of HTLV-1 proviral DNA.

CASE

A 58-year-old male patient visited the another hospital due to erythematous skin plaques and nodules in both extremities without associated B symptom or hepatosplenomegaly. Skin biopsy was performed and lymphoma was suggested. Two months later he was referred to our hospital. Right testicular mass was found during staging work-up and right orchiectomy was performed.

The patient had diabetes mellitus, which was controlled with glibenclamide 1/2 tablet. He had frequently visited Japan for business during the last several years. He had immigrated to the USA (Los Angeles) several years ago.

Examination of the peripheral blood showed WBC of 13300/mm^3, Hb of 13.3 g/dl, platelet count of 210000/mm^3 and ESR 39 mm/hr. No atypical cells were present in peripheral blood or bone marrow. The serum LDH

Table 1. Immunohistochemical analysis of lymphoma tissue

Antibodies	Synonym	Result
CD30	Ki-1, Ber-H_2	Positive
CD45	LCA (Leukocyte common antigen)	Positive
$CD45R_o$	UCHL-1	Weakly positive
CD43	MT-1	Positive
CD15	Leu-M1	Positive
CD20	L26 (Pan-B)	Negative
CD68	(macrophage/monocyte)	Negative
EMA	Epithelial membrane antigen	Negative

level was 902 U/L, calcium level, 8.5 mg/dl, uric acid, 4.3 mg/dL and β_2-microglobulin, 1.37 μg/ml. Anti-EBV antibody was negative. The HTLV-1 antibody titer was over 1 : 256 by particle heme agglutination method. The CT scans revealed no enlarged lymph nodes in the mediastinal, intra-abdominal, or retroperitoneal para-aortic areas and less than 1 cm sized cervical lymph nodes on right side.

Histopathologic examination of the removed testicle and skin showed diffuse dense infiltrates of pleomorphic large lymphoma cells compatible with anaplastic large cell lymphoma (Fig. 1 and 2). The results of immunohistochemical studies are summarized in Table 1. The tumor cells were positive for CD45 (LCA), CD15, CD30 (Fig. 3A), and CD43 (MT-1) (Fig. 3B) antibodies and negative for epithelial membrane antigen (EMA), CD20 (L26) and CD68 antibodies. CD45Ro (UCHL-1) was weakly positive. The presence of HTLV-1 proviral genome was investigated by PCR previously described (10, 11). The target sequences used were bases 7302-7504 of HTLV-1 *pX* gene and the amplification primers were 5'-CCC ACT TCC CAG GGT TTG GAC AGC G-3'(7302-7362), 5'-CTG TAG AGC TAG GCC GAT AAC GCG-3'(7504-7481). The HTLV-1 *pX* region was detected in the tissue of biopsied skin nodule and peripheral blood mononuclear cells (Fig. 4).

He was treated for ATL/L, stage IVA. Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone and bleomycin was performed during the first two cycles, and was switched to F-MACHOP (5-fluorouracil, methotrexate, cytarabine, cyclophosphamide, doxorubicin, vincristine, prednisolone) due to progression of skin lesions. Currently he went into partial remission after five cycles of F-MACHOP.

DISCUSSION

In our case, excised testicle and skin nodules showed diffuse, dense infiltrates of large lymphoma cells. The tumor cells were positive for CD30 (Ki-1 antigen) and showed T-cell phenotype. On the other hand, serologic examination for HTLV-1 antibody was positive and the

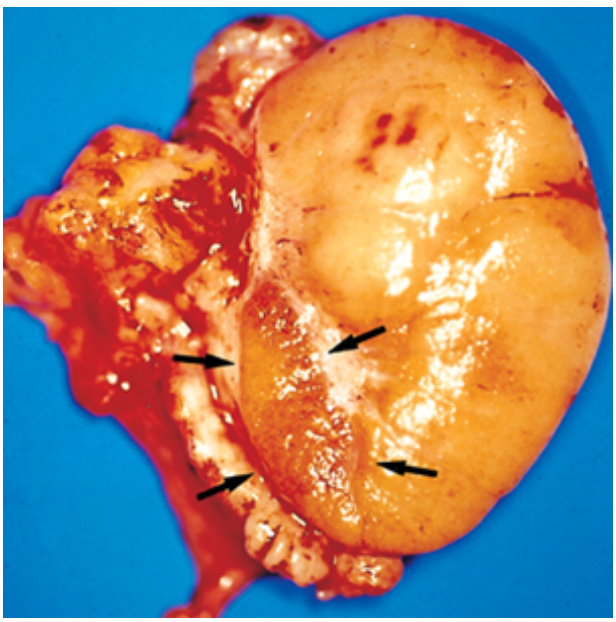


Fig. 1. Cut surface of right testis showing almost total replacement by yellowish homogeneous tumor with fish flesh appearance. Remaining normal testicular tissue is focally present (Arrows).

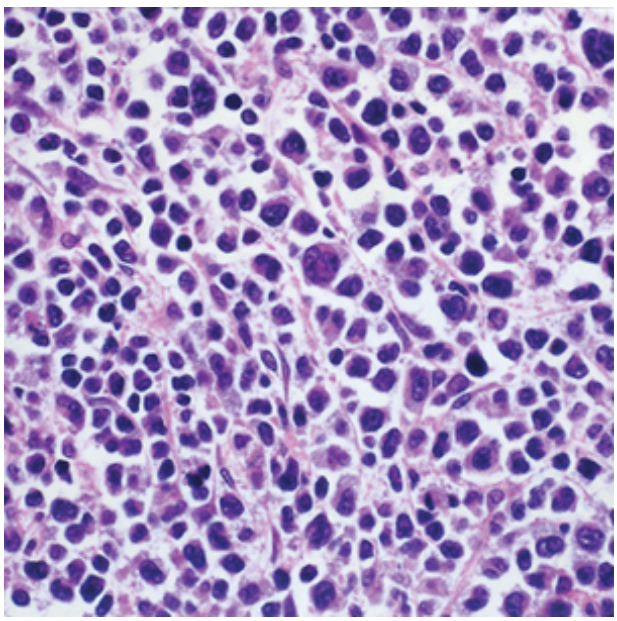


Fig. 2. The tumor cells are markedly irregular in size and shape, showing large cells with hyperchromatic pleomorphic multiple nuclei, prominent nucleoli and abundant eosinophilic cytoplasm as well as small cells with scanty cytoplasm (H&E).

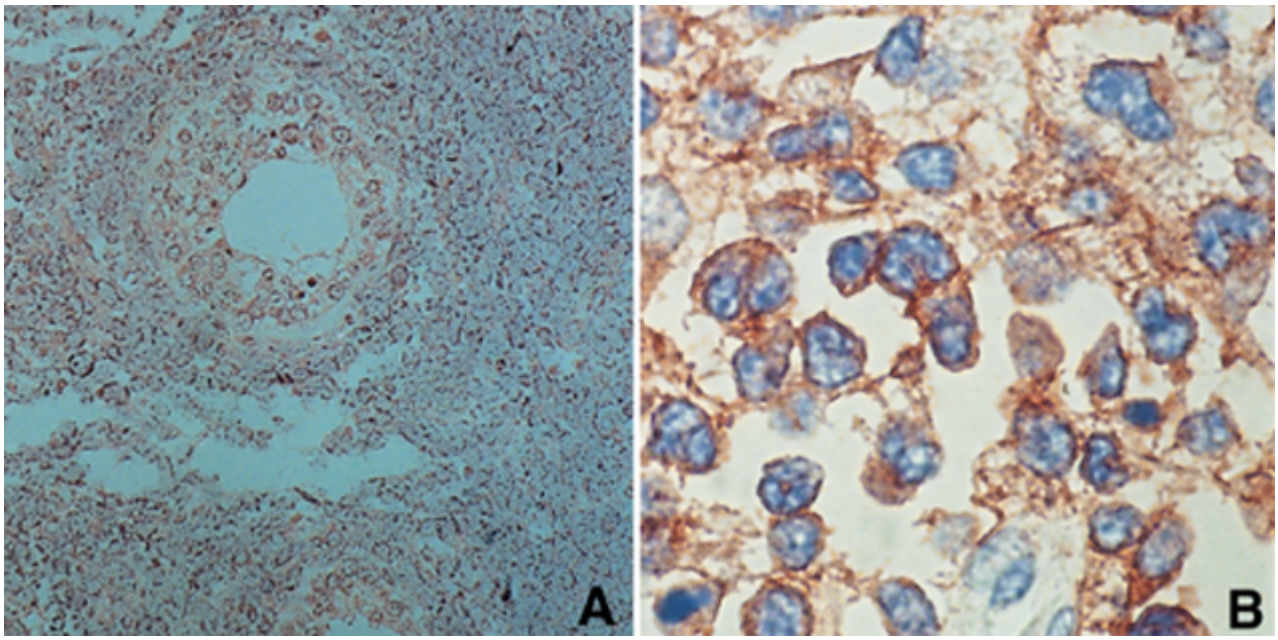


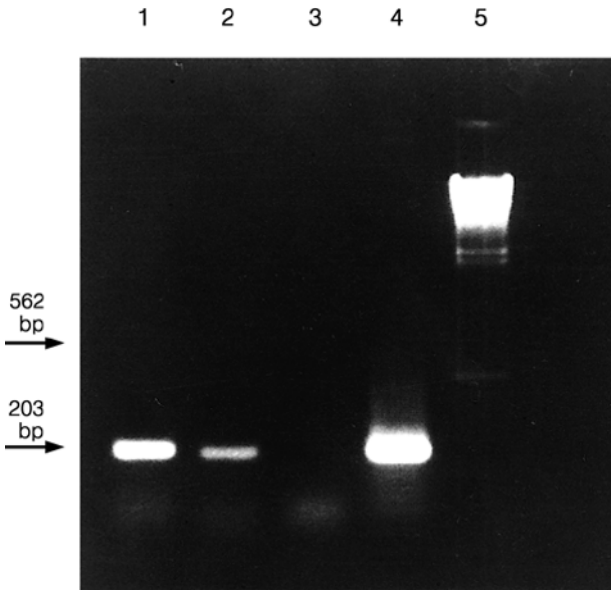
Fig. 3. (A) CD30 (Ber-H2) shows positive reaction in cell membranes. (B) Tumor cells showing positive reaction with anti-MT-1 (CD43).

integrated HTLV-1 proviral DNA was detected in tumor cells of the skin lesion and peripheral blood mononuclear cells. These results indicate that this case could also be categorized as HTLV-1 associated ATL/L, an entity proposed by Uchiyama et al. (3).

CD30 positive ALCL is characterized by proliferation of activated anaplastic lymphoid cells, which usually show T-cell phenotype and Ki-1 positive immunoreactivity. However, CD30 (Ki-1 antigen) which is a member of the tumor necrosis factor/nerve growth factor receptor superfamily (12), is not specific for ALCL and is observed consistently in Hodgkin's disease and variably in other forms of peripheral T-cell lymphoma, and its expression was induced by HTLV-1 *in vitro* (2).

ATL/L caused by HTLV-1 virus is usually characterized by lymphadenopathy, hepatosplenomegaly, skin rash, leukemic change, and hypercalcemia with aggressive clinical course to a fatal termination in prototype (3). However, ATL/L shows diverse clinical features and can be divided into four subtypes : smoldering, chronic, lymphoma, and acute type (13).

Since our patient did not show hypercalcemia, hepatosplenomegaly or leukemic changes, this case is different from those commonly seen of ATL/L but similar to some cases of ATL/L previously reported (4~6). Takeshita et al. (6) reported 21 patients with CD30 (Ki-1) positive ATL/L. These patients showed histologically anaplastic large cell lymphoma or pleomorphic type and frequently presented with extranodal tumors and rarely with leukemic changes, bone marrow



Lane 1. Sample DNA from tumor tissue
Lane 2. Samlpe DNA from PBMC
Lane 3. Negative control
Lane 4. Positive control
Lane 5. λ phage Hind III cut size marker

Fig. 4. PCR DNA amplicates using specific primer for HTLV-1 *pX* gene. DNA from tissue of biopsied skin nodule (Lane 1) and peripheral blood mononuclear cells (PBMC) (Lane 2) showed the same amplified fragments with positive control of HTLV-1 (Lane 4).

involvement and hypercalcemia. They proposed this anaplastic large cell type of ATL/L had distinctive clinical and immunohistological features in comparison with the previously reported cases of ATL/L or anaplastic large cell lymphoma.

Our patient showed extranodal tumor which was immunohistologically anaplastic large cell with CD30 positive and T-cell phenotype, and integration of HTLV-1 proviral DNA *pX* region was detected in tissues of skin nodule and peripheral blood mononuclear cells by PCR. The *pX* region of HTLV-1 might have a close relationship to neoplastic transformation in ATL/L, and HTLV-1 proviral *pX* is the most reliable target for detection of HTLV-1 (14). Thus, his clinical and immunohistological features are compatible with this anaplastic large cell type of ATL/L.

Epidemiologically, the HTLV-1 virus is endemic to Southern Japan, the Caribbean area, and Central Africa and has been rarely involved in the Korean patients with leukemia and lymphoma. Only three cases of ATL/L have been reported in Korea (10,11,15), and on epidemiologic studies, Lee et al. (16) reported 0.25% positivity of serum antibodies of HTLV-1 without evidence of ATL/L and Kim et al. (17) revealed 0.16% positive rate of serum anti-HTLV-1 in blood donors. No case of noncutaneous, non-adult type malignant T cell lymphoma related to HTLV-1 has yet been reported in Korea (18).

This patient had frequent trips to Japan in his fourth and fifth decades, and now he is a resident in the United States. The route of transmission was obscured but it is suggested that he was infected from HTLV-1 endemic region.

ATL/L shows very poor prognosis despite the most aggressive chemotherapy, and reported median survival time is 9.0 months (13). In CD30 positive anaplastic large cell type of ATL/L, the overall survival in patients with diffuse CD30 positive ATL/L is better than that of CD30 negative ATL/L patients. Further study is necessary to clarify the relationship of HTLV-1 infection and CD30 antigen expression with ATL/L in view of prognosis and treatment.

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