

TAL1 재배열 음성인 t(1;5)(p32;q31)을 보인 T 림프모구백혈병 1예

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A Novel Translocation t(1;5)(p32;q31) that Was Not Associated with the TAL1 Rearrangement in a Case of T Lymphoblastic Leukemia/Lymphoma

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Chromosome 1 band p32 (1p32) aberrations are common in T lymphoblastic leukemia/lymphoma (T-ALL/LBL). Two types of 1p32 aberrations include translocations with different partners and sub-microscopic interstitial deletion. Both aberrations are known to result in *TAL1* gene deregulation. The t(1;5)(p32;q31) is a rare translocation of 1p32 in T-ALL. We now present the second case of t(1;5)(p32;q31) in T-ALL, which was present as a primary cytogenetic abnormality, with a review of the relevant literature. Interestingly, neither the translocation of the *TAL1* gene nor aberrant expression of TAL1 protein was detected by fluorescent *in situ* hybridization (FISH) and by immunohistochemical staining in this case. (*Korean J Lab Med* 2009;29:199-203)

Key Words : T-ALL, t(1;5)(p32;q31), *TAL1* gene

INTRODUCTION

Recurrent chromosomal translocations are frequently associated with a diagnosis and prognosis of hematologic malignancies [1]. In cases of leukemia, translocations of chromosome 1 band p32 (1p32) or a cryptic interstitial deletion at 1p32 are specifically associated with T lymphoblastic leukemia/lymphoma (T-ALL/LBL) [2, 3]. Translocations with various partners such as 14q11, 7q35 or 3p21 occur in

approximately 3% of T acute lymphoblastic leukemia (T-ALL) cases, but the t(1;5)(p32;q31) translocation has been reported only in two cases [3-7]. We present here an additional case of t(1;5)(p32;q31). One of the previously reported cases had t(1;5)(p32;q31) as a secondary abnormality and immunophenotyping was not described; therefore, this is the second case of T-ALL with t(1;5)(p32;q31) as a primary cytogenetic abnormality.

CASE REPORT

1. Clinical features

A 49-yr-old Korean male patient was admitted for evaluation of left side pleural effusion in February 2007. Computed tomography images showed multiple enlargement of

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the cervical, supraclavicular and mediastinal lymph nodes. A biopsy was performed on a left neck node, and complete effacement with CD3 and TdT positive small to medium sized blasts was identified. The bone marrow (BM) showed normal cellularity with 4.2% blasts. A complete blood cell count (CBC) measured a Hb concentration of 17 g/dL, a platelet count of $270 \times 10^9/L$, and a white blood cell (WBC) count of $9.4 \times 10^9/L$. These findings were consistent with a diagnosis of T-lymphoblastic lymphoma (T-LBL). After 11 months, blasts were noted in a peripheral blood smear, although the patient underwent five cycles of chemotherapy. A CBC mea-

sured a Hb concentration of 7.9 g/dL, a platelet count of $93 \times 10^9/L$, and a WBC count of $0.85 \times 10^9/L$ (58% lymphocytes, 2% monocytes, 4% eosinophils, and 36% blasts). The BM aspirates showed hypocellularity (20%) and an increase of blasts up to 85.0% (Fig. 1). The blasts were positive for the expression of CD5, CD7, CD33, CD34, CD45, and HLA-DR by flow cytometric analysis, and were positive for the expression of CD3 and TdT as determined by immunohistochemical staining. The diagnosis was revised to T-ALL. The patient immediately received remission induction chemotherapy, but failed to achieve remission. Five months

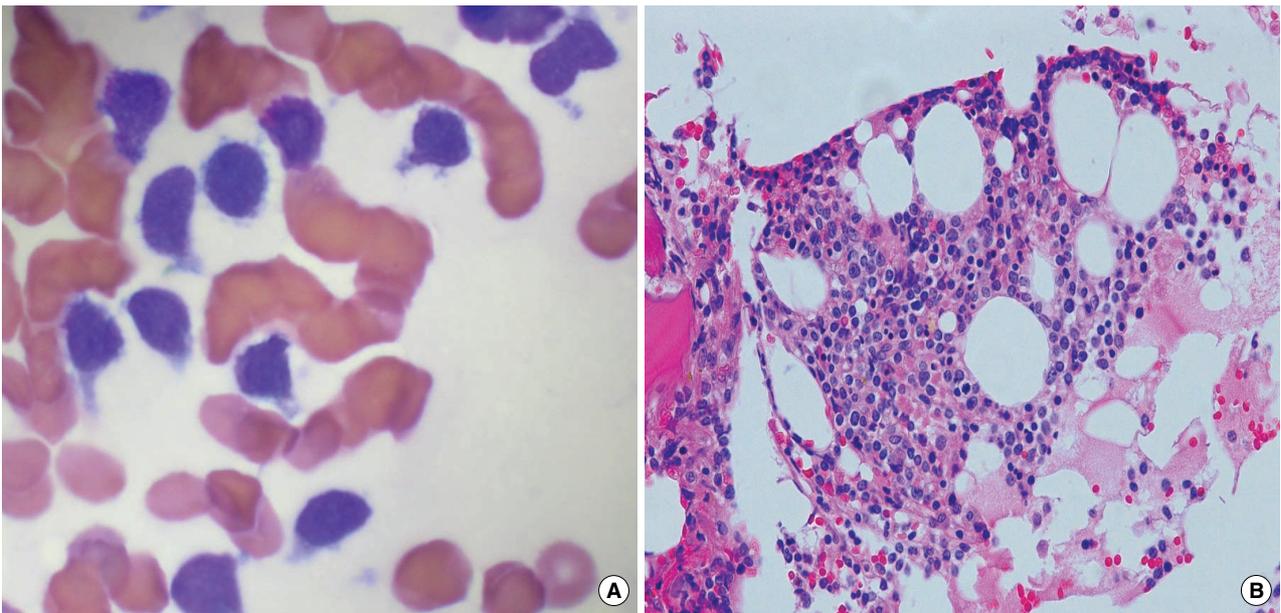


Fig. 1. (A) The bone marrow aspirates (Wright stain, $\times 1,000$) and (B) biopsy (hematoxylin and eosin stain, $\times 200$) showed an increase of small to medium sized blasts.

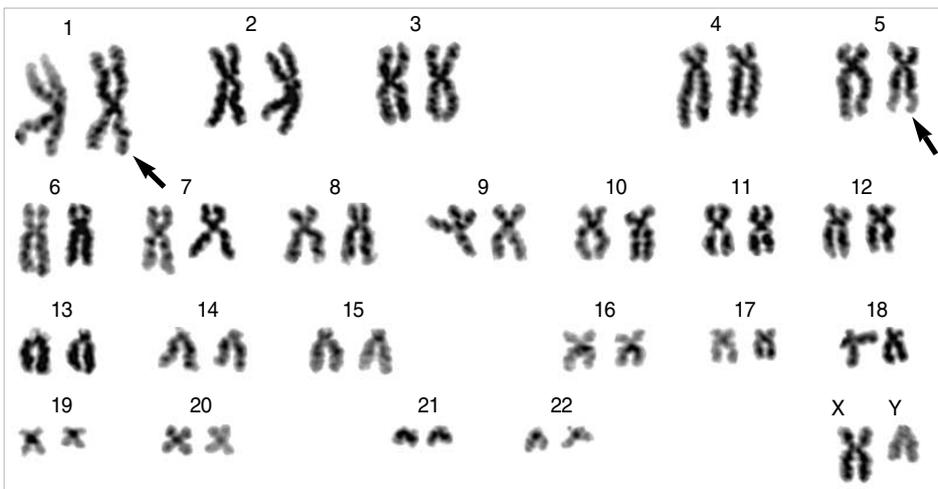


Fig. 2. The representative karyotype showed 46,XY,t(1;5)(p32;q31). Translocation chromosomes are indicated by arrows (GTG banding, $\times 1,000$).

later, the patient died due to renal failure and metabolic acidosis.

2. Conventional cytogenetic analysis and FISH analysis

Cytogenetic analysis was performed using 24-hr unstimulated cultures and synchronized high-resolution cultures

with BM specimens obtained at the time of diagnosis of T-ALL. The chromosomes were analyzed with GTG-banding, and the karyotype was described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. The karyotype was 46,XY,t(1;5)(p32;q31)[8]/46,idem,del(6)(q22)[3]/46,XY[1] (Fig. 2).

FISH analysis was performed with the use of a *SIL-TAL1*

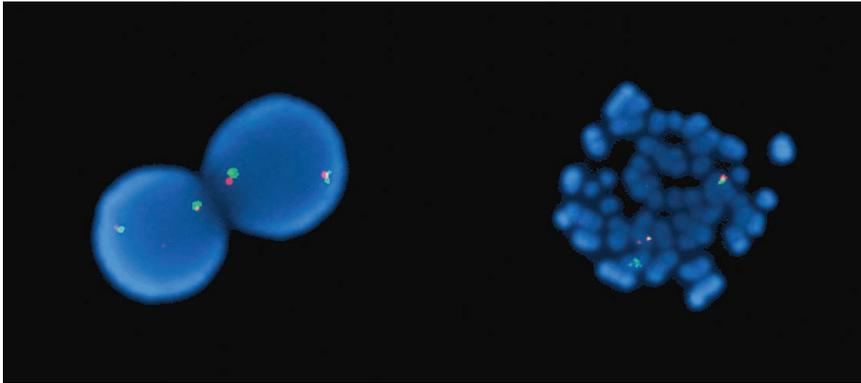


Fig. 3. The *TAL1* gene translocation or submicroscopic deletion was not detected by FISH (× 1,000).

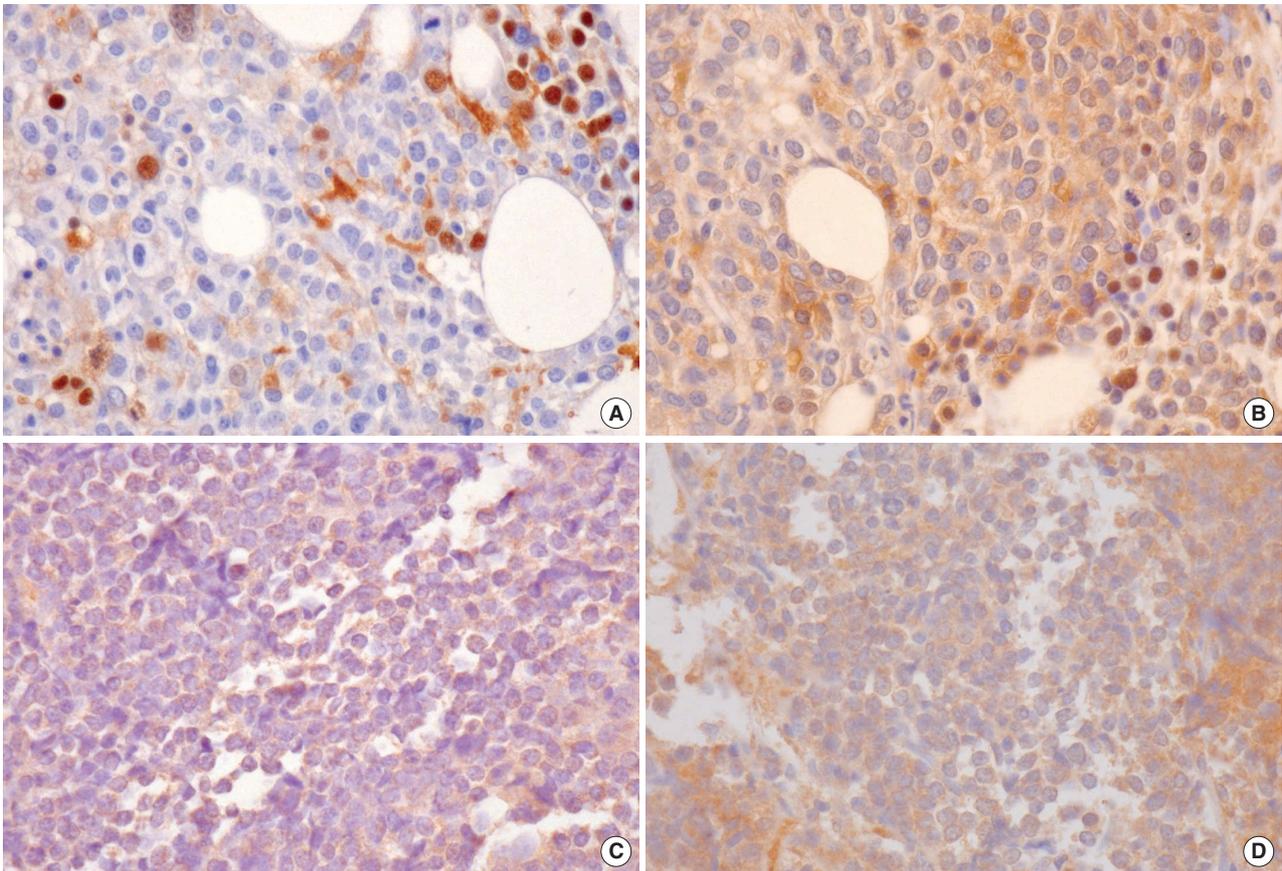


Fig. 4. Immunohistochemical stainings for *TAL1* were negative. (A) 2TL242 on bone marrow, (B) BTL73 on bone marrow, (C) 2TL242 on lymph node, (D) BTL73 on lymph node (× 400).

split-signal FISH DNA probe (DAKO, Glostrup, Denmark) according to the manufacturer's instructions that is designed for the detection of both types of *TAL1* gene aberrations in a single FISH test. In brief, the upstream FISH probe is positioned in the region that is deleted during a *SIL-TAL1* fusion, and in cases with *SIL-TAL1* fusion genes by submicroscopic interstitial deletion, one separate green signal and one co-localized signal are observed. The downstream probe is positioned downstream of the *TAL1* breakpoints. The various forms of *TAL1* translocations result in a split-signal. Two co-localized signals are present in a normal situation without a *TAL1* aberration [8]. Two-hundred interphase cells were scored, and a translocation or deletion was not detected (Fig. 3).

3. Immunohistochemical staining for TAL1 protein

TAL1 protein expression was investigated with BM of the leukemic phase and lymph nodes obtained at the time of the initial diagnosis by the use of immunohistochemical staining for BTL73 and 2TL242 using a peroxidase antibody polymer method. Monoclonal antibodies were generously supplied by Dr. K. Pulford (John Radcliffe Hospital, Oxford, UK). The staining was considered as positive only when nuclear positivity was observed in the blast cells [9]. Immunohistochemical staining demonstrated a negative finding for the BM and lymph nodes of this case, although positivity of erythroid cells confirmed the staining efficacy (Fig. 4). Further molecular analysis of this rearrangement was not possible due to limited patient material.

DISCUSSION

The chromosomal region 1p32 is non-randomly translocated with the 14q11 or 7q35 chromosomal region, where the T cell receptor (TCR) genes are mapped in T-ALL [3, 4, 10]. Additionally, another translocation partner, such as 3p21, and a submicroscopic interstitial deletion of 1p32 have been reported in T-ALL. Thus, rearrangements of 1p32 could account for a recurrent cytogenetic abnormality of T-ALL [5, 11]. The *TAL1* gene (also called *SCL* or *TCL5*) on chromo-

somal region 1p32 is known as the causative gene. The *TAL1* gene codes for a transcription factor with a basic helix-loop-helix (bHLH) motif. The *TAL1* protein is normally expressed by hematopoietic precursors, by megakaryocytes and by cells of an erythroid lineage but not by normal T cells [9]. *TAL1* is deregulated by a translocation or more frequently by a deletion; both types of rearrangements separate the coding exons structurally or functionally from the 5' regulatory sequences (*SIL* gene) and lead to aberrant *TAL1* mRNA and *TAL1* protein expression in T lymphoblastic cells [6].

In the present case, T-ALL presented with a rare translocation of 1p32, t(1;5)(p32;q31). After a review of the relevant literature, we found only two cases with t(1;5)(p32;q31) that have been reported. Both cases were patients with ALL, but one patient had t(1;5)(p32;q31) as a secondary change in addition to t(8;14)(q11.2;q32). Generally, secondary cytogenetic changes are indistinct in a role for leukemogenesis and as immunophenotyping was not described in this case, the pathogenetic role of t(1;5)(p32;q31) was not clear [7]. The other reported case of T-ALL with t(1;5)(p32;q31) was a 31-yr-old male who had a high WBC count and 85% blasts in the BM. *TAL1* mRNA and *TAL1* protein were aberrantly expressed by T-lymphoid blasts. Autologous BM transplantation was carried out 28 weeks after diagnosis, and the patient continued in complete remission over 43 months from the time of the initial diagnosis [6]. In the present case, t(1;5)(p32;q31) was the primary cytogenetic abnormality in T-ALL. For a cytogenetic aberration, 'recurrent' is defined where the abnormality has been previously described in at least one other case, and 'rare' is defined where the abnormality has been previously defined in less than 30 cases [12]. It appears that t(1;5)(p32;q31) is a rare but recurrent cytogenetic abnormality of T-ALL. However, unlike the previously reported case, a *TAL1* gene rearrangement or aberrant *TAL1* protein expression was not demonstrated in the present case. The clinical features were also different. In the previous case, the patient had a good response to chemotherapy and a long-term survival. In the present case, the patient failed to achieve remission in spite of intensive chemotherapy and survival was short. Whereas *TAL1* rearrangements have been associated with a trend to good outcomes

in T-ALL [13, 14], this case with a *TAL1* rearrangement-negative 1p32 translocation demonstrated a poor outcome.

In summary, t(1;5)(p32;q31) is a rare but recurrent cytogenetic abnormality of T-ALL/LBL. Because of its rarity, the role of t(1;5)(p32;q31) for the pathogenesis and the response to therapy for T-ALL is not clear. As the present case did not show a *TAL1* rearrangement or expression of *TAL1* protein, and some other genes clustered at 1p32 such as *BLYM*, *EPS15*, *CDKN2c*, and *JUN* are potential candidates for involvement in leukemogenesis [15], additional case reports and more studies are needed to demonstrate putative genes.

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