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초현미경적 1p33 결실로 인한 *STIL-TAL1* 융합을 동반한 T림프모구백혈병 1예

A Case of T-Lymphoblastic Leukemia with Submicroscopic 1p33 Deletion Resulting in *STIL-TAL1* Fusion

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T-lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy associated with poor outcomes. The genetic background of T-ALL is widely heterogeneous and the *TAL1* gene is overexpressed in approximately half of all cases. A submicroscopic interstitial deletion on chromosome 1p33 results in *STIL-TAL1* fusion, causing inappropriate overexpression of *TAL1*, which promotes T cell leukemogenesis. T-ALL with *STIL-TAL1* exhibits distinct characteristics, such as a mature cortical T cell immunophenotype, low incidence of *NOTCH1* mutation, privileged association with *PTEN* inactivation, deletion of 6q14–q16, *MYC* translocation, high leukocyte count, poor response to treatment, and low event-free survival. However, the clinical relevance and prognostic value of this rearrangement remain unclear. Here, we report the first case of T-ALL with a 1p33 deletion resulting in *STIL-TAL1* fusion in Korea, which was detected by reverse transcriptase-polymerase chain reaction and confirmed by chromosomal microarray analysis.

Key Words: T-lymphoblastic leukemia, 1p33 deletion, *STIL-TAL1* fusion, Reverse transcriptase-polymerase chain reaction, Microarray

INTRODUCTION

T-lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy that results from the malignant transformation of progenitors of T cells. T-ALL accounts for 10–15% of pediatric and 25% of adult ALL cases [1, 2] and is associated with a poor outcome [3]. The genetic background of T-ALL is widely heterogeneous as it is caused by the co-occurrence of multiple genetic abnormalities [1]. Therefore, molecular cytogenetic diagnosis is not currently adopted for T-ALL, and no integrated tests are available to clinically identify the broad spectrum of related genes and alternative molecular mechanisms [1].

TAL1 is a classic oncogene identified in chromosomal translocations in acute leukemia and is an important transcription factor that forms a key regulatory circuit [4]. A submicroscopic deletion on chromosome 1p33 results in *STIL-TAL1* fusion (*STIL* is also known as *SIL*), causing inappropriate overexpression of *TAL1*, which promotes T cell leukemogenesis [3, 4]. *STIL-TAL1* fusion has been suggested to be a likely founder or truncal event, with other common genetic lesions including *CDKN2A* loss, *PTEN* mutation or loss, and *NOTCH1* mutation occurring as secondary subclonal events in *STIL-TAL1* positive T-ALL [5]. However, the clinical relevance and prognostic value of this rearrangement remain unclear.

In this study, we identified *STIL-TAL1* fusion in a patient with T-ALL using reverse transcriptase-polymerase chain reaction (RT-PCR) and confirmed a 1p33 deletion using chromosomal microar-

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ray analysis (CMA). To our knowledge, this is the first report of T-ALL with a 1p33 deletion resulting in *STIL-TAL1* fusion in Korea.

CASE

A 36-year-old man with chest discomfort and petechiae in both legs was referred to our emergency department. Laboratory results showed a leukocyte count of 197.6×10^9/L, hemoglobin level of 111 g/L, and platelet count of 16×10^9/L. Peripheral blood smears revealed 93% blasts (Fig. 1A). The bone marrow (BM) aspirate smear showed 93.5% blasts of small to medium size, with round or slightly cleaved nuclei (Fig. 1B). An immunophenotyping analysis revealed the blasts were positive for cytoplasmic CD3 (cCD3), CD3 (sCD3), CD5, CD7, CD38, and TdT. However, these cells did not express CD10, CD19, CD20, CD22, cCD22, cCD79a, CD13, CD33, CD14, CD64, CD117, or cytoplasmic MPO, suggesting T-ALL. Multiplex RT-PCR with HemaVision (DNA Diagnostic A/S, Risskov, Denmark) revealed a 191-bp *STIL-TAL1* fusion transcript (Fig. 2A, B). The karyotype was 46,XY,del(6)(q21q23)[8]/46,XY[13] (Fig. 3A). Molecular analyses using Sanger sequencing revealed negative results for *NPM1, CEBPA, FLT3-ITD/TKD*, and *Kit* mutations. Next-generation sequencing (NGS) of DNA using an Illumina MiSeqDX platform and a custom-designed ALL panel revealed a *NOTCH1* mutation, which is considered a variant of uncertain significance (VUS). Since the 1p33 deletion resulting in *STIL-TAL1* fusion is a submicroscopic deletion, a microarray analysis was performed to confirm this. A CMA using the CytoScan DX Assay (Thermo Fisher Scientific Inc, Frederick, USA) based on the GRCh37/hg19 assembly showed a 63-kb heterozygous deletion at 1p33 (Fig. 3B) with additional copy number abnormalities, as follows: arr 1p33(47,700,108–47,763,403)×1 [VOUS], arr 6q14.1q16.1(77,124,674–95,680,018)×1 [P], arr 7p14.1(38,293,949–38,395,208)×0 [VOUS], arr 7p34(142,016,358–142,493,639)×1 [VOUS], arr 9p21.3(21,828,109–21,989,103)×0 [P], and arr 9p24.3p13.1(192,128–40,087,758)×2 hmz [VOUS]. Induction chemotherapy was administered to the patient. The follow-up study of BM one month later showed complete hematologic (0.6% blasts), cytogenetic (normal karyotype), and molecular remissions without *STIL-TAL1* fusion transcript (Fig. 2C).

DISCUSSION

The *TAL1* gene is overexpressed in approximately half of T-ALL cases as a result of chromosomal translocations, intrachromosomal rearrangements, or somatic mutations [4]. Translocation-induced *TAL1* dysregulation is rarer than microdeletion-induced dysregulation. A submicroscopic interstitial deletion on chromosome 1p33 causes the 5′ untranslated region of *STIL* to fuse with the coding part of *TAL1* [3, 4]. The deletion places *TAL1* expression under the control of the *STIL* promoter, resulting in inappropriate overexpression of *TAL1*, which promotes T cell leukemogenesis [3, 4]. The *STIL-TAL1* fusion gene has been reported in 15–25% of pediatric and young adult T-ALL cases, but much less frequently in older T-ALL patients [6]. A previous study in India found *SIL-TAL1* fusion in 4/26 (15.4%) pediatric and none of the 7 adult T-ALL cases [7].

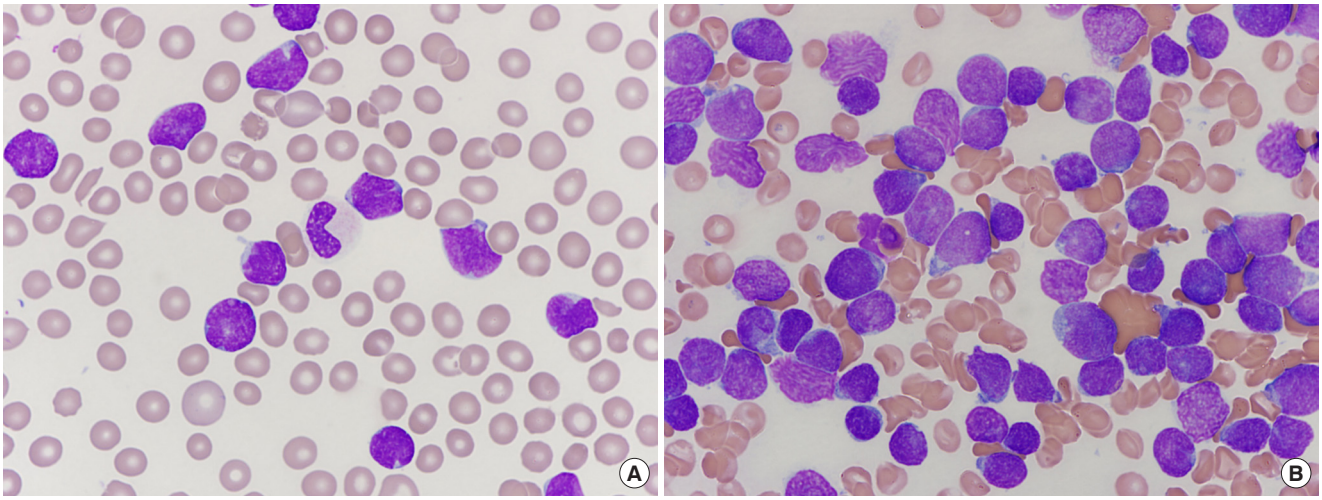

Fig. 1. Morphology of blasts in a peripheral blood smear (A) and bone marrow aspirate smear (B).

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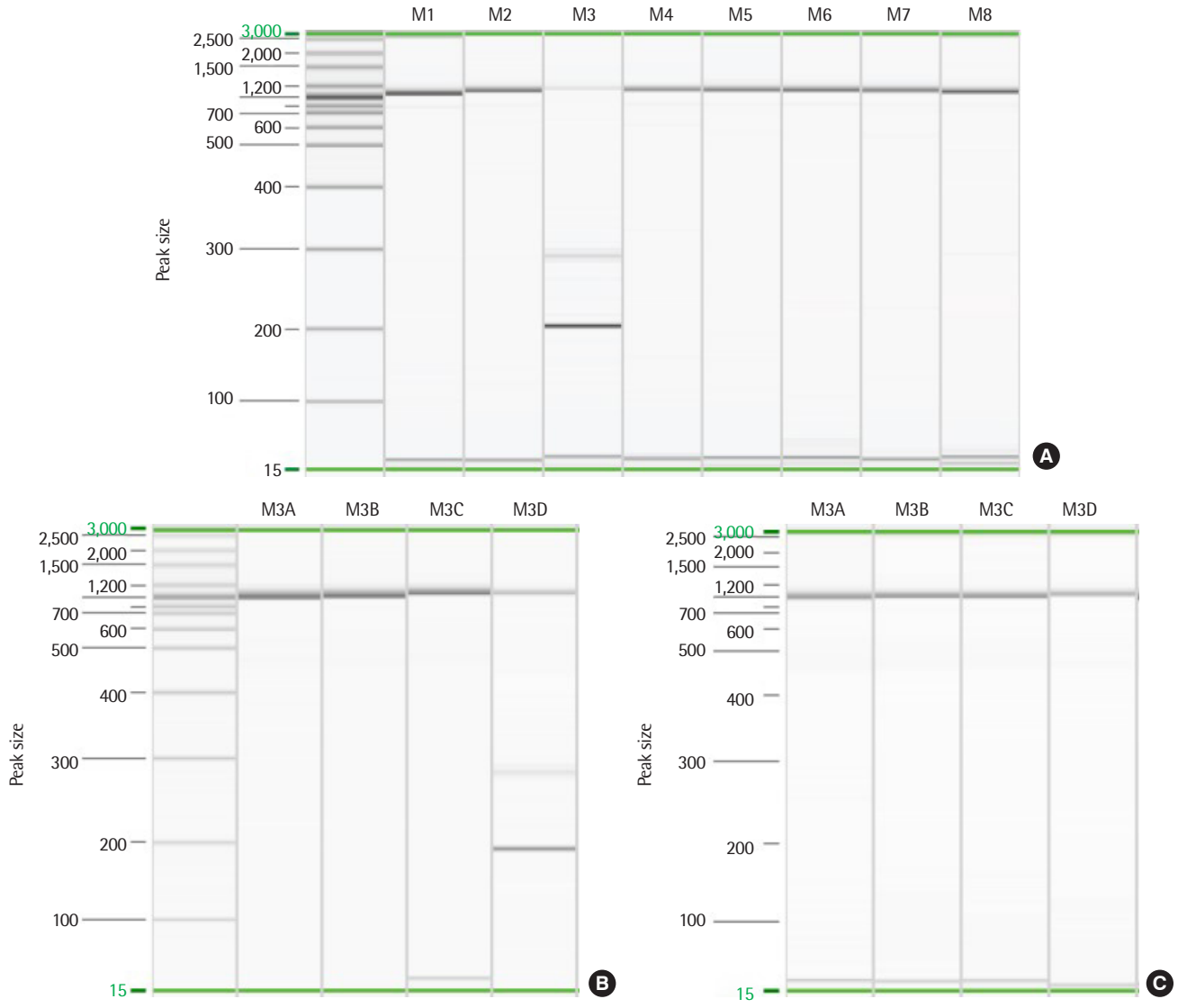

Fig. 2. Detection of the *STIL-TAL1* fusion transcript resulting from 1p33 deletion by multiplex RT-PCR. The screening kit produced a single band in the M3 lane (A), and the split-out kit produced a single 191-base pair band in the M3D lane at diagnosis (B). The split-out kit revealed no band in the M3D lane in the follow-up study one month later (C).

Chromosome deletions, as a mechanism for fusion gene formation, are mostly submicroscopic. Hence, they are not detected by cytogenetic analyses; however, they can be detected by array comparative genomic hybridization and/or high-throughput sequencing [6, 8]. In 1990, two independent research groups working on T-ALL used southern analysis to detect an approximately 90-kb interstitial deletion in 1p33 which caused *STIL-TAL1* fusion, and this was the first description of a fusion gene resulting from an interstitial, submicroscopic deletion [6]. Yu et al. [8] performed a microarray analysis and found a submicroscopic deletion of approximately 80-kb in 1p33 (47,461,779–47,547,806 based on the hg18 assembly) leading to a *STIL-TAL1* fusion in 9 of the 22 pediatric T-ALL patients. In the present case, the *STIL-TAL1* fusion was first detected by multiplex RT-PCR. CMA confirmed a 63-kb deletion in 1p33 (47,700,108–47,763,403 based on the GRCh37/hg19 assembly).

Furthermore, T cell receptor rearrangement (deletion at 7p14.1 and 7q34) and biallelic deletion of *CDKN2A* (deletion at 9p21.3) were suspected based on the CMA results. *NOTCH1* and *CDKN2A* play a surprising role, as they are altered in more than half of T-ALL cases [1, 9]. Activation of *NOTCH1* signaling affects the specification and development of thymocytes, while *CDKN2A* haplo-

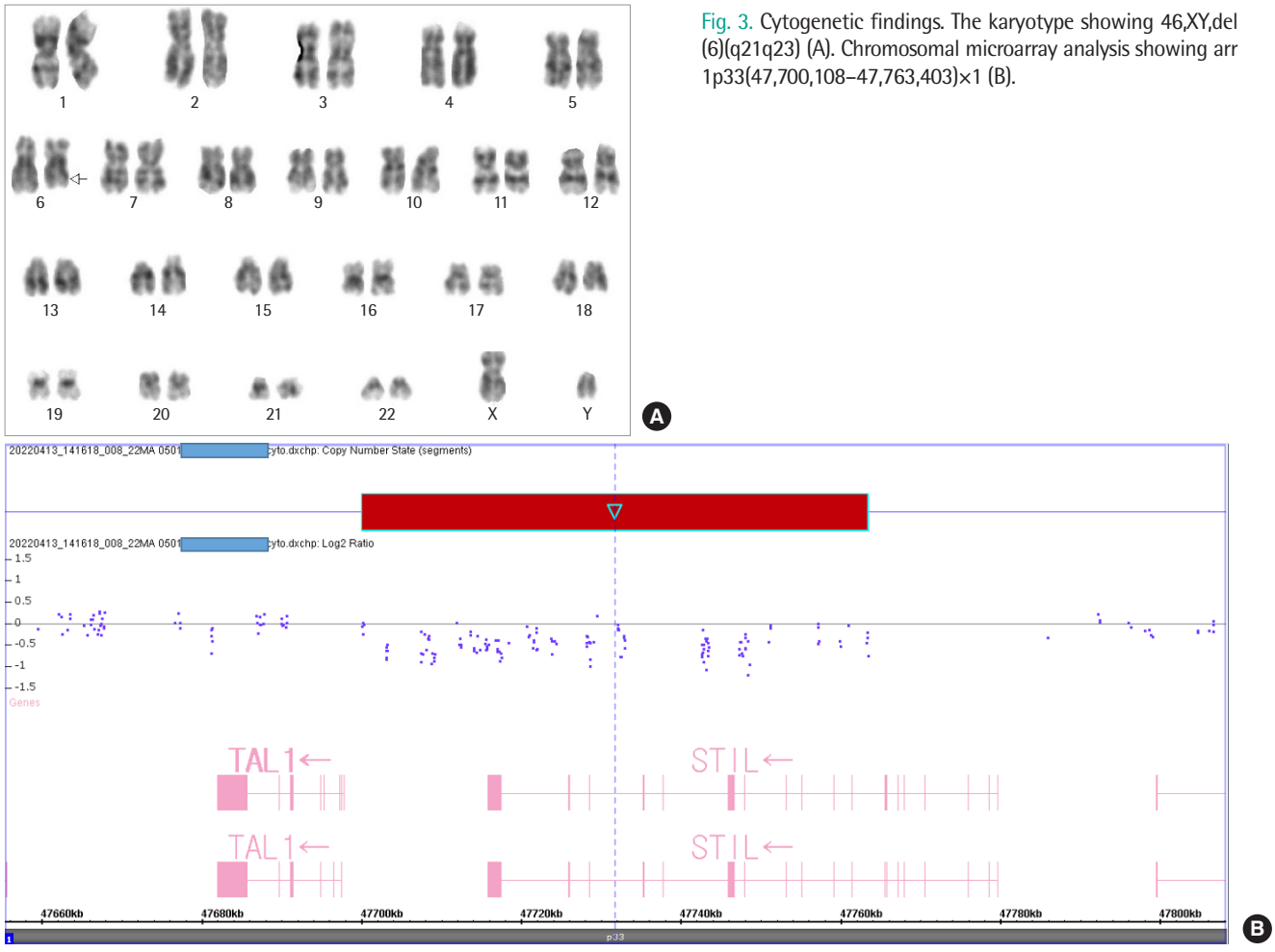

Fig. 3. Cytogenetic findings. The karyotype showing 46,XY,del (6)(q21q23) (A). Chromosomal microarray analysis showing arr 1p33(47,700,108–47,763,403)×1 (B).

insufficiency/inactivation promotes cell cycle progression [1]. The present study revealed that PCR, NGS, and microarray analysis allow for a more comprehensive assessment of genetic abnormalities in T-ALL.

T-ALL with aberrations of *TAL* shares the immunophenotype indicative of arrest of mature cortical T cell development (sCD3 positive) and the same gene expression features as a low incidence of *NOTCH1* mutation (~40% of cases), a privileged association with *PTEN* inactivation, deletion of 6q14–q16, and *MYC* translocation, all of which act as poor prognostic markers [1]. Previous studies have reported that *STIL-TAL1* is associated with adolescence, higher leukocyte counts at diagnosis, poor response to treatment, and slightly lower event-free survival than T-ALL without *STIL-TAL1* [3]. However, the clinical relevance and prognostic value of this rearrangement remain unclear, as different studies have reported favorable or unfavorable results in *STIL-TAL1*-positive patients [3, 6, 10]. The present case also exhibited distinct features similar to those mentioned previously, such as sCD3 expression, a *NOTCH1* mutation, 6q14.1–6q16.1 deletion, and a very high leukocyte count at diagnosis. However, a follow-up study of BM one month later showed complete remission, indicating a good response to induction chemotherapy.

According to Zhao et al. [11], the *STIL-TAL1* expression in 16 patients changed from negative before transplantation to positive at a median of 77 days (30–281 days) after transplantation, and 15 (93.8%) of them eventually experienced relapse. Their study demonstrated the reliability of *STIL-TAL1* fusion transcripts as excellent minimal residual disease (MRD) markers. In the present study, expression of the *STIL-TAL1* fusion transcript changed from positive at diagnosis to negative at complete remission a month later, supporting its role as a reliable marker for MRD.

In conclusion, we report the first case in Korea of T-ALL with a 1p33 deletion resulting in *STIL-TAL1* fusion. More studies are required, including extensive cytogenetic and molecular analyses to

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identify novel therapeutic targets and to determine the pathophysiology, laboratory characteristics, clinical significance, and MRD monitoring of this gene rearrangement and other interstitial deletions/fusion genes.

요 약

T림프모구백혈병(T-ALL)은 공격적인 악성 혈액 종양으로 좋지 않은 예후를 보인다. T-ALL은 다양한 유전이상과 관련이 있으며, 약 절반 정도에서 *TAL1* 유전자의 과발현이 나타난다. 염색체 1p33의 미세 결실은 *STIL-TAL1* 재배열을 생성하고 이는 *TAL1* 유전자의 과발현을 유발하여, T 세포에서 백혈병으로 진행을 야기하게 된다. T-ALL에서 *STIL-TAL1* 재배열이 존재하는 경우, 성숙 T 세포의 면역표현형, 낮은 *NOTCH1* 유전자 돌연변이 발생률, *PTEN* 유전자 비활성화와의 연관성, 6q14-q16의 결실, *MYC* 유전자 전위, 진단 시의 높은 백혈구 수와 치료에 불량한 반응 등과 같은 독특한 특성을 보인다. 하지만, *STIL-TAL1* 재배열의 임상적 의의와 예후적 의미에 대해서는 아직 명확하게 알려져 있지 않다. 본 연구에서는 역전사효소-중합효소 연쇄반응(RT-PCR)과 염색체 마이크로어레이 분석(chromosomal microarray analysis)으로 확인한 1p33 결실로 인한 *STIL-TAL1* 재배열이 존재하는 T-ALL을 국내에서 첫 번째 증례로 보고하고자 한다.

Conflicts of Interest

None declared.

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