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Case Report

T-cell lymphoblastic leukemia/lymphoma with t(7;14)(p15;q32) [TCRγ-TCL1A translocation]: a case report and a review of the literature

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Abstract: A 22-year-old man sought medical advice for a swelling in the right side of the neck in December 2011. Histopathological examination of the lymph node biopsy initially suggested reactive lymphadenitis, on account of the only sparse presence of tumor cells. Bone marrow examination was performed in February 2012 revealed findings consistent with a diagnosis of T-cell lymphoblastic leukemia/lymphoma (T-LBL), and the patient was begun on remission induction therapy. The bone marrow showed an immature thymocytic pattern: cytoplasmic CD3$^+$, surface CD3$^-$, CD5$^+$, CD4$^-$, and CD8$^-$. Re-assessment of the lymph node specimens revealed the same phenotype of the cells in the lymph node as that of the blasts in the bone marrow. In addition, a chromosomal aberration t(7;14)(p15;q32) was noted. The lymph node biopsy specimens were examined by paraffin-embedded tissue section-fluorescence in situ hybridization (PS-FISH), which revealed a fusion signal of T-cell receptor (TCR)γ gene (7p15) with T-cell leukemia/lymphoma 1A (TCL1A) gene (14q32.13). There have been at least 10 reported cases of T-LBL with t(7;14)(p15;q32), including the present case. However, this is the first reported case in which TCRγ-TCL1A translocation was confirmed by FISH.

Keywords: T lymphoblastic leukemia/lymphoma, t(7;14)(p15;q32), TCL1A, TCR gamma, immature thymocytic pattern

Introduction

The most frequent cytogenetic abnormalities in T lymphoblastic leukemia/lymphoma (T-LBL) are T cell receptor gene (TCRα, TCRβ, TCRγ, and TCRδ) translocations with a variety of partner genes [1]. Some of the TCR gene translocation partners are Lim only domain 2 (LMO2) (15%), T-cell acute leukemia 1 (TAL1) (11%), and T-cell leukemia homeobox 1 (TLX1) (25%). TCR-T-cell leukemia/lymphoma 1A (TCL1A) translocation is extremely rare (< 1%), and among the TCR genes, there have been only one reported case each with verified TCRα [2] and TCRβ [3] translocations, and no case of TCRγ translocation has yet been reported.

We encountered a case of T-LBL with t(7;14)(p15;q32). At least 10 cases of T-LBL with t(7;14)(p15;q32) have been reported to date. In some of the cases with t(7;14)(p15;q32), the abnormality involved TCRγ (7p15) and 14q32 (immunoglobulin heavy chain; IgH) [4]. In the case documented herein, however, there was no evidence of the IgH-JH (14q32.33) split signal, as assessed by paraffin-embedded tissue section-fluorescence in situ hybridization (PS-FISH). Therefore, this report describes a T-LBL patient with reciprocal translocation of the TCRγ gene at 7p15 and the TCL1A gene at 14q32.13 as demonstrated for the first time by PS-FISH.

Case report

A 22-year-old man, presented with a chief complaint of fever and right cervical lymph node enlargement. His past history included infantile

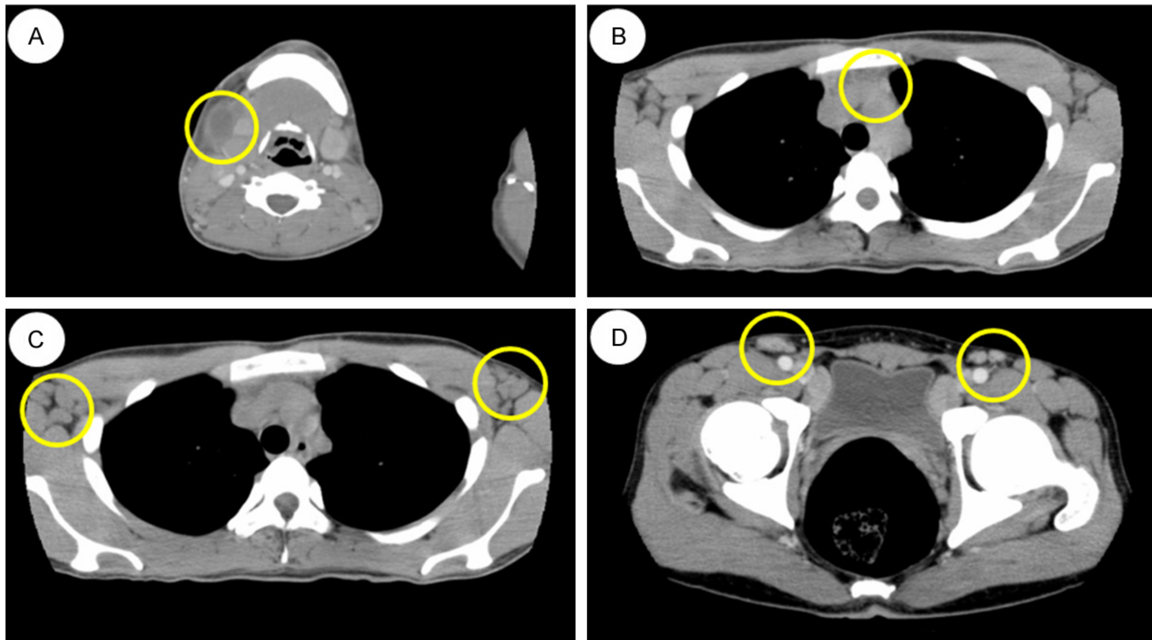


Figure 1. Computed tomography (CT) image. The right cervical (A), upper anterior mediastinal (B), bilateral axillary (C), and bilateral inguinal (D) lymph nodes are enlarged (yellow open circles).

asthma and mild intellectual disability. He sought medical advice for a swelling that he had begun to feel in the right side of the neck since December 2011. As he was febrile (37°C) and computed tomography (CT) revealed enlarged lymph nodes ranging up to about 5 cm in diameter in the right cervical, bilateral axillary, anterior mediastinal and bilateral inguinal regions, biopsy of the right inguinal lymph node was performed. Initially, based solely on the findings on hematoxylin-eosin (H&E)-stained sections, reactive lymphadenitis was suspected, as only sparse tumor cells were present. The patient was subsequently followed with periodic checkups, especially in view of an observed tendency for the enlarged lymph nodes to contract. In February 2012, re-enlargement of the right cervical lymph nodes was noted, and blasts were detected in the peripheral blood; therefore, a bone marrow examination was performed, which led to a diagnosis of T-LBL, and the patient was admitted to our hospital.

Findings on physical examination at admission included height 171 cm, body weight 60.3 kg, and body temperature 37.5°C. Multiple enlarged right cervical lymph nodes (measuring up to about 5 cm in diameter), axillary lymph nodes (about 2 cm in diameter), and inguinal lymph nodes (about 1 cm in diameter) were palpable. There was no hepatosplenomegaly.

Hematologic examination on admission revealed a markedly decreased total white blood cell count of 1.2×10^9/L and a neutrophil count of 0.36×10^9/L, with 16.5% blasts. The red blood cell count was slightly decreased, and no abnormalities of the platelet count or blood coagulation profile were noted. In the blood biochemical and serologic tests, the serum level of soluble interleukin-2 receptor (sIL-2R) was elevated (5760 U/mL), and serum C-reactive protein (CRP) was slightly elevated (0.8 mg/dL). CT at admission revealed enlargement of the cervical, anterior mediastinal, bilateral axillary, and bilateral inguinal lymph nodes (**Figure 1**). Bone marrow examination revealed nucleated cell hypoplasia (10000/μL), and myeloperoxidase-negative blasts accounted for 86% of the nucleated cells. Histopathologic examination of bone marrow biopsy specimens failed to be immunostained, as they had lost their immunogenicity as a result of the decalcification process (data not shown). As can be seen in **Figure 2**, flow-cytometry (FCM) analysis of the bone marrow cells showed the marrow blasts to be weakly positive for CD34, CD2, and CD7, negative for CD3 (probably positive for intracellular CD3), CD4, and CD8, but weakly positive for

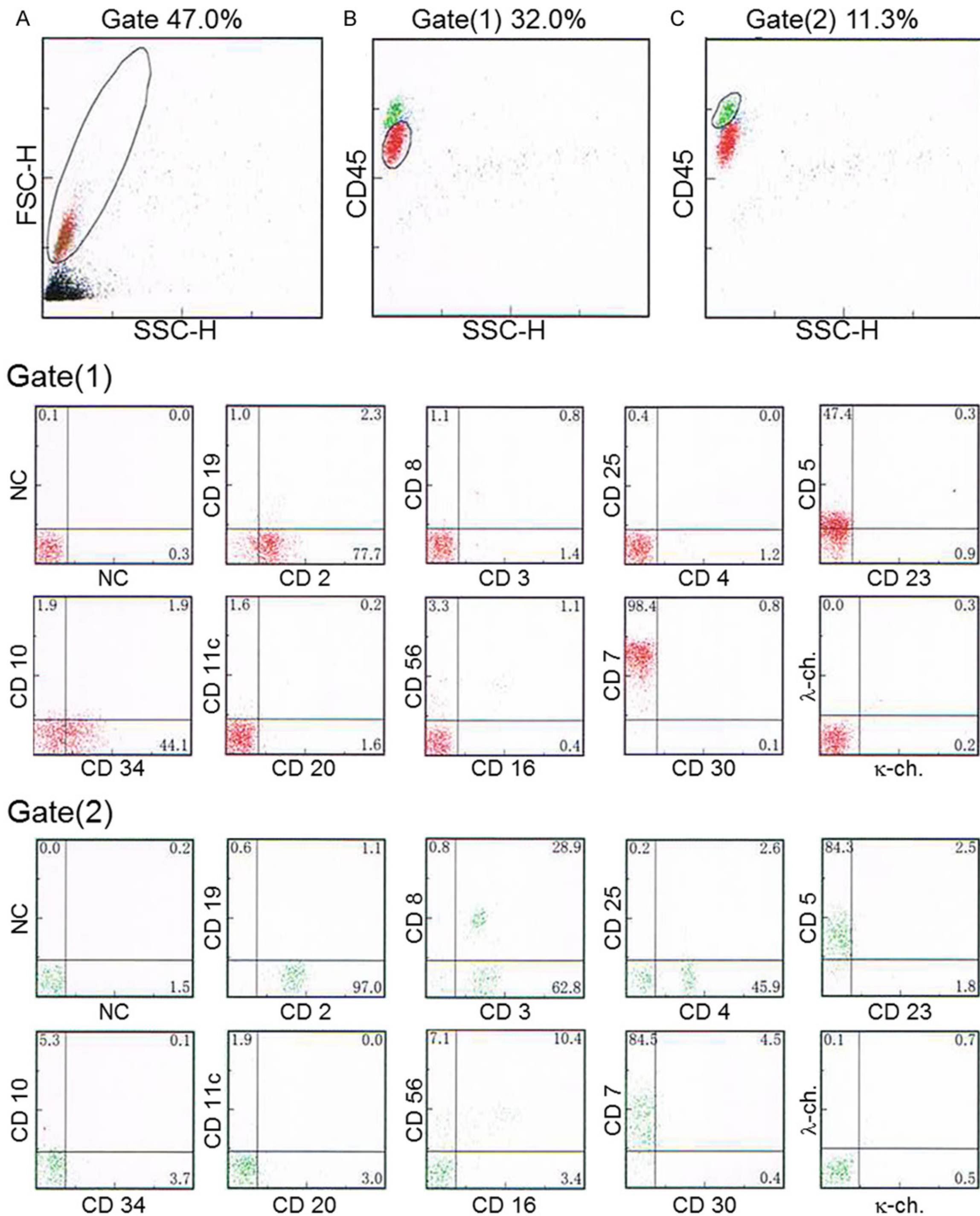


Figure 2. Flow-cytometric analysis of the bone marrow cells. A subpopulation of cells are weakly positive for CD2, negative for CD3, negative for CD4, weakly positive for CD5, strongly positive for CD7, negative for CD8, and weakly positive for CD34 was identified in Gate 1, where weakly CD45-positive blastoid series were collected. The majority of the strongly CD45-positive cells in Gate 2 were considered to be reactive, mature T cells.

CD5 and CD34. Chromosomal analysis of the bone marrow cells was unfortunately infeasible due to poor growth of the marrow cells in vitro. Southern blot analysis of the bone marrow failed to demonstrate any gene rearranged band of the IgH-JH or TCR-Cβ1. Thus, a diagnosis of T-LBL was made.

Rechecking of histopathologic sections of the biopsy specimens obtained from the enlarged

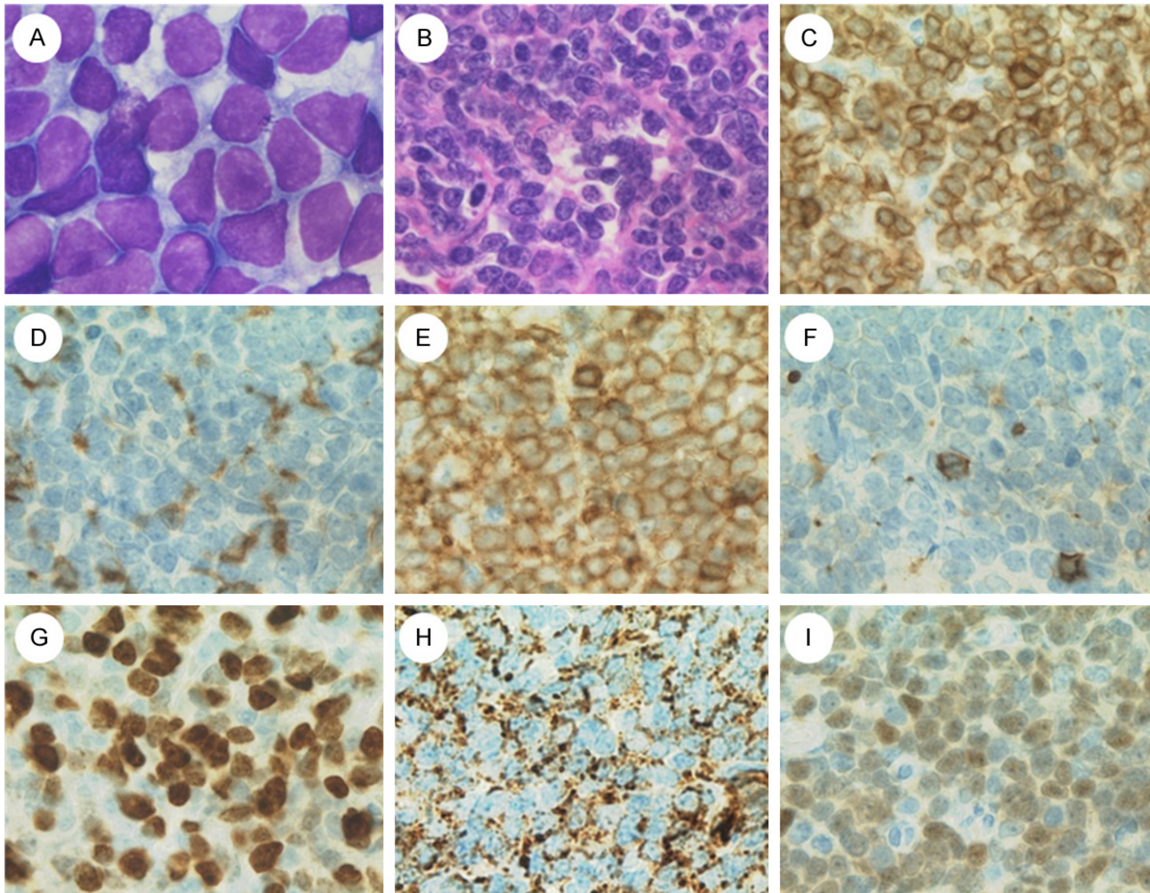
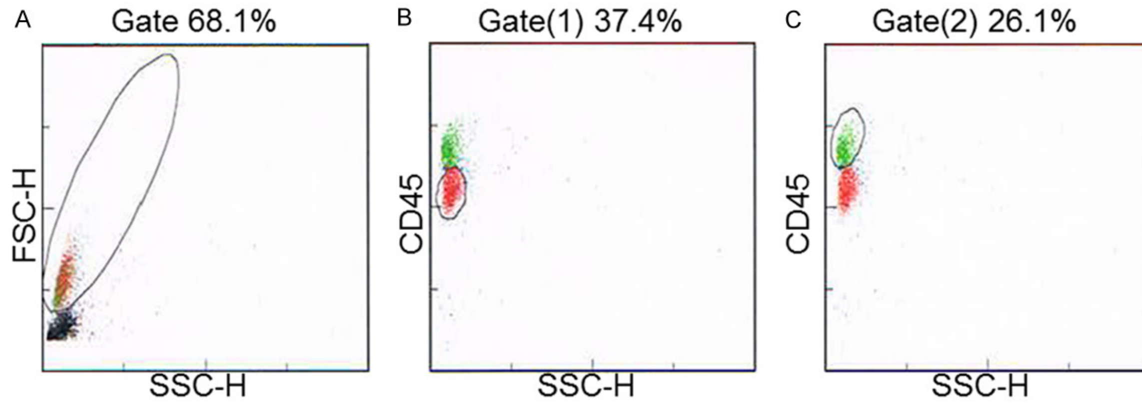
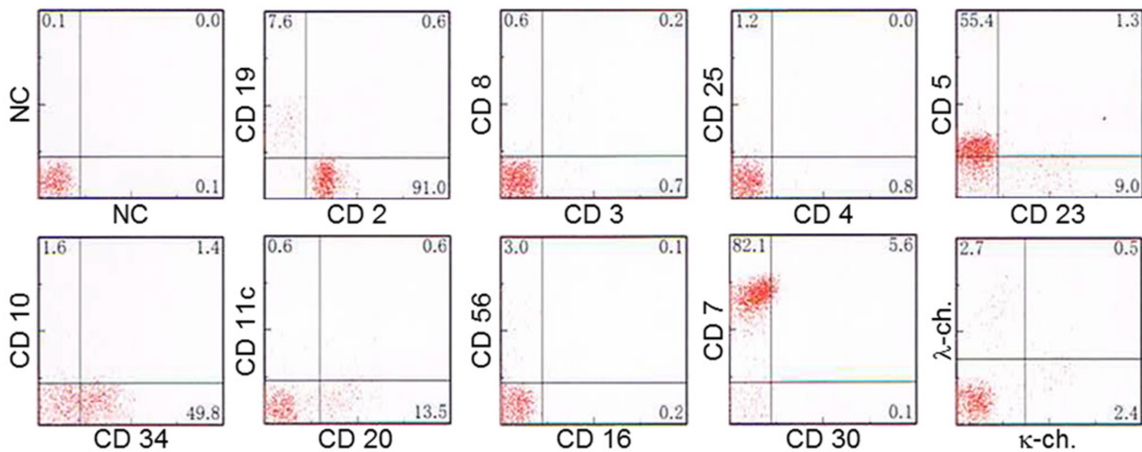


Figure 3. Immunohistochemistry of the T-lymphoblastic leukemia/lymphoma cells in the lymph node. A: Wright-Giemsa-stained bone marrow (× 1000) showing a fine nucleoreticulum and a large number of blasts with a high nuclear-cytoplasmic (NC) ratio. Sections B to H show blast-rich areas in the infiltrated lymph nodes. B: Hematoxylin-eosin (H&E)-stained bone marrow (× 600) showing a large number of blasts with a high NC ratio. C: CD3-positive. D: CD4-negative (granulocytes etc., are positive). E: Weakly CD5-positive (strongly positive cells are normal T cells). F: CD8-negative (positive cells are normal T cells). G: Ki-67-positive. H: Weakly CD34-positive. I: Weakly Terminal deoxynucleotidyl transferase (TdT)-positive.

lymph nodes in December 2011 revealed, similar to the case for the marrow blasts, that the lymph node cells were positive for intracellular CD3 (but negative for cell surface CD3 on FCM), negative for CD4 and CD8, weakly positive for CD5, CD34, and intracellular terminal deoxynucleotidyl transferase (TdT), and highly positive for Ki-67 (**Figure 3**). Results of FCM of the lymph node cells were similar to those of the bone marrow cells (**Figure 4**). Chromosomal analysis with G-banding staining revealed t(7;14)(p15;q32) in three of 14 lymph node cells. The same biopsied lymph node was subjected to PS-FISH. No IgH split signal was detected initially; therefore, by reference to the literature, the case was considered to be TCL1A (14q32.13) rather than IgH (14q32.33). 7p15 was estimated to belong to TCRγ. As expected, subsequent exploration by PS-FISH revealed a fusion signal of the TCRGC2 and TCL1A genes.

Details of the PS-FISH test procedure are given below. The TCRGC2 gene probes employed were bacterial artificial chromosome (BAC) clone RP11-354A7, RP11-121A8 and RP11-867H7, and the probes used for the TCL1A/TCL1B gene were RP11-809D14, RP11-164H13 and RP11-483K13. The BAC DNA of the TCRGC2 gene was labeled with Cy3 (red), and that of the TCL1A/TCL1B gene was labeled with isocyanate (green). Paraffin sections were deparaffinized, processed with 0.1% pepsin/0.1N HCL at 37°C for 6 minutes, rinsed in distilled water, and dried. FISH probes were then applied to the sections, and the sections and probes were heated for denaturation on a hot





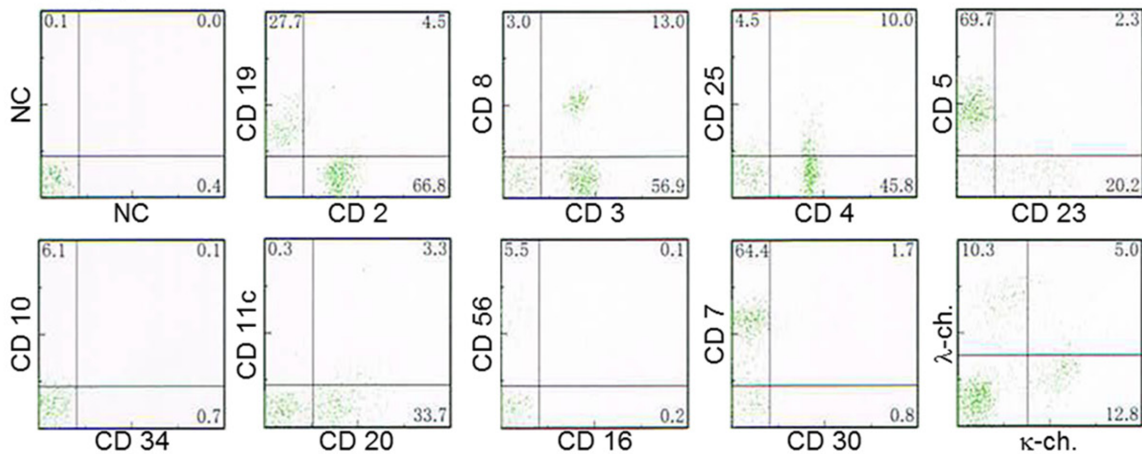


Figure 4. Flow-cytometric analysis of the T-lymphoblastic leukemia/lymphoma cells in the lymph node. Blast cells are weakly positive for CD2, negative for CD3, negative for CD4, weakly positive for CD5, strongly CD7-positive, negative for CD8, and positive for CD34 were demonstrated in the Gate (1) region, where weakly CD45-positive cells predominate. The majority of the CD45-positive cells in Gate (2) region are reactive, mature T cells.

plate at 90°C for 10 minutes, followed by hybridization at 37°C overnight. The hybridized sections were stringent-washed with 50% formaldehyde/2x saline-sodium citrate (SSC) and with 1x SSC at 37°C. The sections were then counterstained with 4',6-diamidino-2-phe-

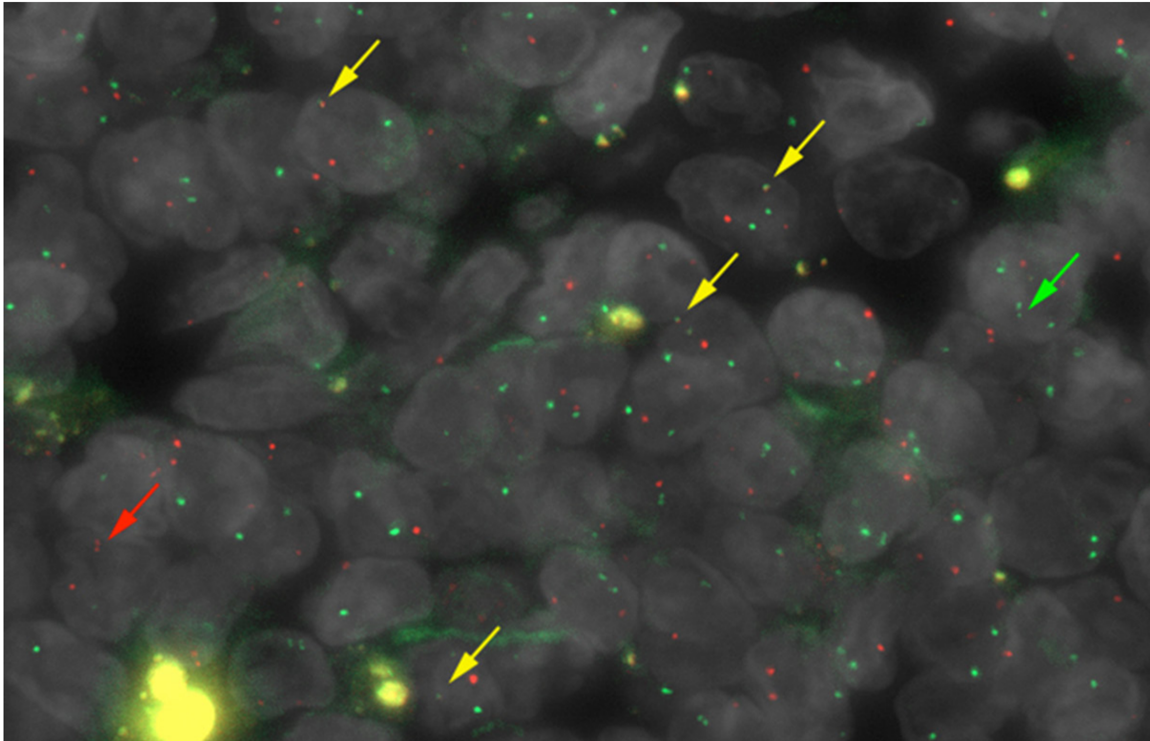


Figure 5. Fluorescence in situ hybridization (FISH) of the TCL1A/TCL1B-TCRγ fusion gene. FISH was performed on paraffin sections prepared from the lymph node biopsy specimens. The bacterial artificial chromosome (BAC) DNA of the TCR GC2 gene was labeled with Cy3 (red), and that of the TCL1A/TCL1B gene was labeled with isocyanate (green), respectively. Therefore, cells indicated by yellow arrows have the fusion gene. At least 14% (3/21) of tumor cells had the TCL1A/TCL1B-TCRγ fusion gene, since 21% of the entire cell population had the chromosomal aberration t(7;14)(p15;q32), although only 3% of the entire cell population was positive for the fusion gene.

nylindole (DAPI) and mounted with an anti-fading agent. Detection of probe signals on tissue sections and analysis of the relevant data were carried out with a Leica CW-4000 System. Photomicrographic images were obtained using a 63x objective lens. The results of PS-FISH assay in the lymph node tissue are presented in **Figure 5**. The lymph node chromosomal aberration t(7;14)(p15;q32) was detected at an approximate frequency of 21% (three of 14 cells), while the incidence of the fusion signal of TCR1A/TCR1B and TCRγ was about 3%; therefore, a TCL1A-TCRγ fusion signal was ultimately noted at an incidence of 14% (3/21) in our patient with T-LBL.

Southern blot analysis of the lymph nodes failed to reveal any band of rearrangements of the IgH-JH or TCR-Cβ1 gene, nor was there any evidence of a rearranged band of the TCR-Jγ and TCR-Jβ1 genes; therefore, the lymph nodes were also diagnosed as T-LBL infiltrates.

Chemotherapy was initiated in accordance with the ALL202-U protocol specified in the Japan Adult Leukemia Study Group (JALSG) for adolescents. Complete remission was verified by bone marrow examination on Day 33 and has since been maintained for about 2 years.

Discussion

T-LBL is a neoplasm composed of immature lymphoblasts of the T cell lineage. The neoplasms with the chromosomal aberration of t(7;14)(p15;q32) was acute leukemia in all the cases documented until now, and there have been at least 12 reported cases, including the present case (**Table 1**). Of the 12 cases reported, eight were from the United States, and four from Japan. The patients were relatively young, with a mean age of 18 years. Peripheral blood cell counts showed decreased white blood cell counts and blasts. The diagnosis was T-LBL in 10 patients, acute myeloid leukemia (AML) in one patient, and pre-B ALL in one patient. Detailed accounts of the condition, such as the phenotypes, were recorded in five cases. Case 11 [5] had a different clinical course because

Table 1. Clinical findings of acute leukemia with t(7;14)(p15;q32)

Case	Country	Age	Sex	WBC (× 10^9/L)	Blast in PB (%)	Diagnosis	Response to therapy	Survival (mo)	Karyotype [No. of Cells]	References
1	Japan	10	F	2.4	0	T-LBL	CR	23+	46, XX, t(6;12)(q21;p13), t(7;14)(p15;q32) [20/30]	[4]
2	Japan	14	M	5.8	0	T-LBL	CR	6+	46, XY, t(7;14)(p15;q32)	[8]
3	Japan	9	M	2.7	0	T-LBL	CR	24+	46, XY, t(7;14)(p15;q32) [9/10]	[9]
4	USA	NA	NA	NA	NA	AML (M2)	NA	NA	46, XX, t(7;14)(p15;q32)	[10]
5	USA	NA	NA	NA	NA	Pre-B LBL	NA	NA	46, XX, t(4;14;7)(q21;q32;p15)	[11]
6	USA	4	F	5.2	NA	T-LBL	CR	12	45, XX, 1(1;2)(p22;p14), t(7;14)(p15;q32), dic(12;18)(p11;p11)	[12]
7	USA	14	F	10.6	NA	T-LBL	CR	12	46, XX, t(7;14)(p15;q32)	[12]
8	USA	NA	NA	NA	NA	T-LBL	NA	NA	46, XX, del(5)(q31), del(6)(q15q23), t(7;14)(p15;q32)	[7]
9	USA	NA	NA	NA	NA	T-LBL	NA	NA	46, XY, inv(5)(p13q14)(p15q11), del(6)(p21.3-22), t(7;14)(p15;q32)	[7]
10	USA	NA	NA	NA	NA	T-LBL	NA	NA	46, XX, t(7;14)(p14;q32), del(9)(q12q22)	[7]
11	USA	55	M	4	NA	T-LBL	NA	1	46, XY, t(7;14)(p15;q32)	[5]
12	Japan	22	M	1.2	16.5	T-LBL	CR	24+	46, XY, t(7;14)(p15;q32) [3/14]	present case

Abbreviations: CR, complete remission; F, female; M, male; NA, not available; PB, peripheral blood; Pre, precursor; T-LBL, T lymphoblastic lymphoma/leukemia.

Table 2. Immunophenotipic analysis of acute leukemia with t(7;14)(p15;q32)

Case	TdT (%)	CD2 (%)	CD3 (%)	cy CD3 (%)	CD4 (%)	CD5 (%)	CD7 (%)	CD8 (%)	CD10 (%)	CD19 (%)	TCRCβ1*	References
1	NA	90.0	8.0	NA	16.0	72.0	NA	3.0	0.0	NA	NA	[4]
2	29.2	4.2	6.0	NA	3.4	6.3	93.9	2.3	7.9	2.3	NA	[8]
3	NA	3.1	2.4	ND	1.0	61.0	95.3	1.0	10.6	54.9	G	[9]
4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[10]
5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[11]
6	-	61.0	NA	NA	NA	77.0	86.0	NA	-	-	NA	[12]
7	53.0	76.0	NA	NA	NA	34.0	84.0	NA	31.0	-	NA	[12]
8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[7]
9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[7]
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	[7]
11	+	-	-	+	-	+	+	-	NA	NA	NA	[5]
12 (LN)	ND	91.6	0.9	NA	0.8	56.7	87.7	0.8	3.0	8.2	G	present case
12 (PB)	23.0	84.6	3.3	69.0	0.6	92.2	98.9	2.5	0.3	5.0	NA	present case
12 (BM)	6.3	80.0	2.2	NA	1.2	47.7	99.2	1.9	3.8	3.3	G	present case

Abbreviations: BM, bone marrow; cy, cytoplasmic; G, germ; LN, lymph node; NA, not available; PB, peripheral blood; R, rearranged; TCR, T-cell receptor; TdT, terminal deoxynucleotidyl transferase; +, positive; -, negative result (< 20% positively); *using southern blot analysis.

of concurrent human immunodeficiency virus (HIV) infection. Three other patients (Cases 1, 2, and 3) responded well to treatment and had a favorable outcome.

T-LBL blasts are intracellular TdT-positive and are frequently positive for CD2, CD3, CD4, CD5, CD7 and CD8. The blasts show a high percentage of cells positive for CD7 and cytoplasmic CD3, among other clusters of differentiation. Review of data from the five cases of T-LBL with t(7;14)(p15;q32), including the case described herein (**Table 2**), revealed an immature thymocytic pattern, i.e. CD7-positive, surface CD3-negative and CD4CD8-double negative in all five cases. In the present case, blasts in the

peripheral blood were surface CD3-negative but were intracellular CD3-positive. It could be assumed that the circulating blasts were positive for cytoplasmic CD3 in all of these cases, although the relevant data were lacking in some cases. Aside from T-LBL, involvement of t(7;14)(p15;q32) has also been reported in a case of AML and a case of B-LBL (**Table 2**).

There is no rearrangement of the TCR gene in most cases of T-LBL, while karyotype abnormalities are seen in 50-70% of T-LBL patients. The most frequent cytogenetic abnormalities are translocations between TCRα or δ on the short arm of chromosome 14 (14q11.2), TCRβ on the long arm of chromosome 7 (7q35), or TCRγ on the short arm of chromosome 7 (7p14-15) and various partner genes [6]. In most instances, transcription of a partner gene is dysregulated under the influence of the transcriptional control region in a TCR locus as a result of the translocation. Heerema *et al*. reported detecting chromosomal aberrations in 103 (61%) of 169 patients with T-LBL, with involvement of TCRβ in 29 patients, while TCRβ was involved in only eight patients, and TCRγ was involved in only four patients [7]. There were nine patients (5.3%) who had a chromosome breakpoint region at 14q32, of whom five had translocations; of these five cases, the translocation was t(7;14)(p14-15;q32) in three patients (2.9%).

TCL1A (14q32.1), TCL1B (14q32.1), AKT1 (14q32.3), and IGHJ (14q32.33) are mainly located in the chromosome 14q32. According to a report by Kaneko and colleagues, their presence might represent a signal of fusion between TCRγ at 7p15 and IgH-JH at 14q32 [4]. However, FISH revealed no evidence of a split IgH-JH signal in our case. In view of this, we assumed that the gene located at 14q32 might be TCL1 rather than IgH-JH. The TCL1 gene is an oncogene located at 14q32.1, which has been reported to have a bearing upon the development of T-cell prolymphocytic leukemia (T-PLL). TCL1A is usually demonstrated in early T cell progenitors ($CD3^-CD4^-CD8^-$) and lymphoid cells of the B lineage, whereas the TCL1B gene is expressed in a wide variety of tissues. It is thus inferred that T-LBL with t(7;14)(p15;q32) develops as a consequence of fusion of the TCL1 gene at 14q32 and TCRγ gene at 7p15, which is valid also for the present case.

The demonstration of translocation of the TCL1A/TCL1B gene at 14q32.1 to the transcriptional region in the TCRγ gene locus at 7p15 in the present patient by genetic analysis based on PS-FISH using TCL1A/TCL1B and TCRγ probes seems to be of profound significance.

Disclosure of conflict of interest

None.

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