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A Case of Adult B Lymphoblastic Leukemia with ider(9)(q10)t(9;22)(q34;q11.2) and der(19)t(1;19)(q23;p13.3)

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In B lymphoblastic leukemia/lymphoma (B-ALL/LBL), t(9;22)(q34;q11.2) and t(1;19)(q23;p13.3) are recurrent cytogenetic abnormalities. The concurrent occurrence of both abnormalities is very rare, and only 3 cases have been previously reported. Here, we report a case of adult B-ALL with ider(9)(q10)t(9;22)(q34;q11.2) and der(19)t(1;19)(q23;p13.3). A literature review revealed that ider(9)(q10)t(9;22) is a rare variant of t(9;22) with a deletion of the short arm of chromosome 9. Fifteen cases of ider(9)(q10)t(9;22) have been reported. This abnormality is specific to precursor B-lymphoid neoplasms, such as B-ALL or B-lymphoid blast phase of CML, and is associated with disease progression or short survival. The cytogenetic abnormality t(1;19) is also specific to B-ALL. In most instances of t(1;19), *TCF3* is fused to *PBX1*; however, a few cases have identical translocations but no *TCF3-PBX1* fusion, as was observed in our patient. We describe the first case of ider(9)(q10)t(9;22) in combination with *TCF3-PBX1* negative t(1;19). The patient underwent imatinib therapy in addition to intensive chemotherapy, but failed to achieve remission. ***(Korean J Lab Med 2010;30:585-90)***

Key Words : *Recurrent cytogenetic abnormalities, B lymphoblastic leukemia, ider(9)(q10)t(9;22), der(19)t(1;19)*

INTRODUCTION

According to the updated WHO classification of tumors of hematopoietic and lymphoid tissues, specific genetic abnormalities are the key defining criteria for B lymphoblastic leukemia/lymphoma (B-ALL/LBL) as well as many myeloid neoplasms. Hyperdiploidy, hypodiploidy, t(9;22)(q34;q11.2), t(v;11q23), t(12;21)(p13;q22), t(5;14)(q31;q32), and t(1;19)(q23;p13.3) are recurrent genetic abnormalities of B-ALL/LBL. These abnormalities are associated with distinctive clinical or phenotypic features, have important prognostic implications, and concurrent occurrence is very rare [1]. Recently, we treated a case of adult B-ALL with ider(9)(q10)t(9;22)(q34;q11.2) and der(19)t(1;19)(q23;p13.3). Only 10 cases of B-ALL and 5 cases of CML in the blast phase have previously been reported with ider(9)(q10)t(9;22); thus, it is a very rare variant of t(9;22) [2-14]. In a conventional cytogenetic study conducted on this patient, der(19)t(1;19) was also observed, and it appeared to be simultaneously associated with 2 types of recurrent abnormalities. However, *TCF3-PBX1* translocation was not identified by FISH or reverse transcriptase PCR (RT-PCR). *TCF3-PBX1* negative t(1;19) is rare and has not been previously reported in Korea. Although they are karyotypically identical, the clinical findings associated with *TCF3-PBX1* negative t(1;19)

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are different from those of *TCF3-PBX1* positive t(1;19) [1, 15]. This is the first report of ider(9)(q10)t(9;22) in combination with *TCF3-PBX1* negative t(1;19).

CASE REPORT

A 45-yr-old Korean female was admitted for the evaluation of bicytopenia found during an ophthalmologic examination in June 2008. A complete blood cell count (CBC) showed a hemoglobin level of 8.5 g/dL, a platelet count of 245×10^9/L, and a white blood cell (WBC) count of 3×10^9/L with 66% segmented neutrophils, 31% lymphocytes, and 3% monocytes. She had experienced a visual disturbance and undergone 2 months of high-dose steroid therapy for the treatment of Vogt-Koyanagi-Harada disease. Five days after the cessation of steroids, her WBC count increased and blasts were observed in the peripheral blood (PB). A second CBC revealed a hemoglobin level of 11.0 g/dL, a platelet count of 249×10^9/L, and a WBC count of 30.83×10^9/L with 25% segmented neutrophils, 7% band form neutrophils, 3% myelocytes, 37% lymphocytes, and 28% blasts. Bone marrow (BM) aspirates showed hypercellularity with 94% blasts, which were uniform in appearance, small in size, and had scanty cytoplasm, and inconspicuous nucleoli (Fig. 1). Flow cytometric analysis revealed that the blasts were positive for CD10, CD19, CD20, CD22, CD13, CD34, CD45, HLA-DR, and TdT. Spleen, liver, and lymph nodes were not palpable on physical examination. Although a cytogenetic analysis was performed using 24-hr unstimulated cultures and synchronized high-resolution cultures from the BM aspirates, few analyzable mitoses with normal karyotype were observed, and the karyotype was 46,XX [7]. However, major *BCR-ABL1* rearrangement (b3a2) was detected by RT-PCR using a Seeplex Leukemia *BCR/ABL* kit (Seegene, Inc., Seoul, Korea) (Fig. 2). The patient underwent chemotherapy and imatinib therapy (400 mg/day) for the treatment of B-ALL with t(9;22)(q34;q11.2);BCR-ABL1 and stayed in remission for 9 months. In March 2009, the major *BCR-ABL1* transcript reappeared, the CBC was normal, and no blasts were observed in the PB. Hematologic relapse occurred in April 2009, and the results of BM aspiration and immunophenotyping were similar to those at the first diagnosis. The karyotype was 46,XX,ider(9)(q10)t(9;22)(q34;q11.2),del(9)(q10),der(19)t(1;19)(q23;p13.3),der(22)t(9;22) [20] (Fig. 3). FISH analyses were performed using the Vysis LSI *BCR/ABL1* dual color (DC), dual fusion (DF) translocation probe and the LSI *TCF3/PBX1* DC, DF translocation probe (Abbott Molecular, Abbott Park, IL, USA). FISH analysis showed 3 fusion signals and 1 green signal in 162 interphase cells with the *BCR/ABL1* DC, DF translocation probe (Fig. 4A), and 3 red signals and 1 green signal in 157 interphase

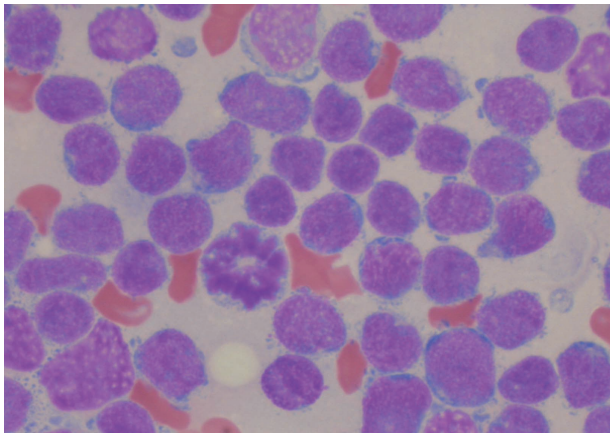

Fig. 1. The bone marrow aspirates showed an increased number of small sized blasts with scanty cytoplasm and inconspicuous nucleoli (Wright stain, ×1,000).

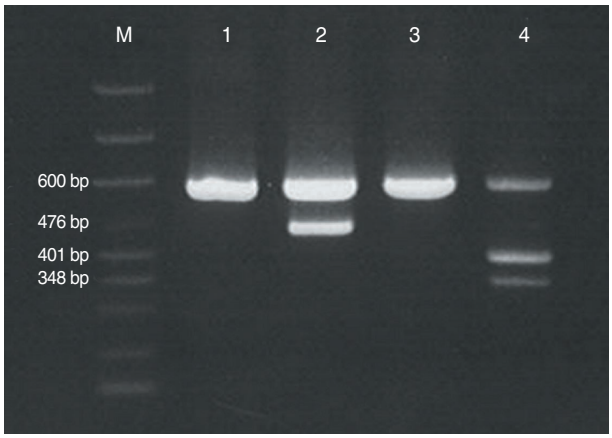

Fig. 2. Reverse transcriptase PCR demonstrated major *BCR-ABL1* gene rearrangement (b3a2) [Lane M, size marker (includes markers for the 600-bp internal control, 476-bp b3a2 fusion transcript, 401-bp b2a2 fusion transcript, and 348-bp e1a2 fusion transcript); lane 1 and 3, negative patients; lane 2, our patient; lane 4, positive control with b2a2 and e1a2 fusion transcripts, provided by the manufacturer].

cells with the *TCF3/PBX1* DC, DF translocation probe (Fig. 4B) out of 200 interphase cells. The result was nuc ish(ABL1 × 3),(BCR × 4),(ABL1 con BCR × 3)[162/200]/(PBX1 × 3,TCF1 × 1)[157/200] according to the international system for human cytogenetic nomenclature 2009 (ISCN 2009) [16]. Multiplex nested RT-PCR was performed using a HemaVision kit (DNA Technology, Aarhus, Denmark). The results were negative for the *TCF3/PBX1* transcript and positive for the *BCR/ABL1* b3a2 transcript (Fig. 5). FISH analyses of samples from the initial diagnosis were performed retrospectively. FISH with the *BCR/ABL1* DC, DF translocation probe showed 3 fusion signals, 1 green, and 1 red signal in 149 of 200 interphase cells. Fusion signals were observed on der(22) and on both arms of ider(9) in mitotic cells (Fig. 4C). FISH with the *TCF3/PBX1* DC, DF translocation probe showed 3 red signals and 1 green signal in 145 of 200 interphase cells; no fusion signal was observed in mitotic cells (Fig. 4D). The patient underwent 3 cycles of intensive chemotherapy with a hyper-CVAD regimen and imatinib therapy (400-600 mg/day). However, she failed to achieve remission and de-

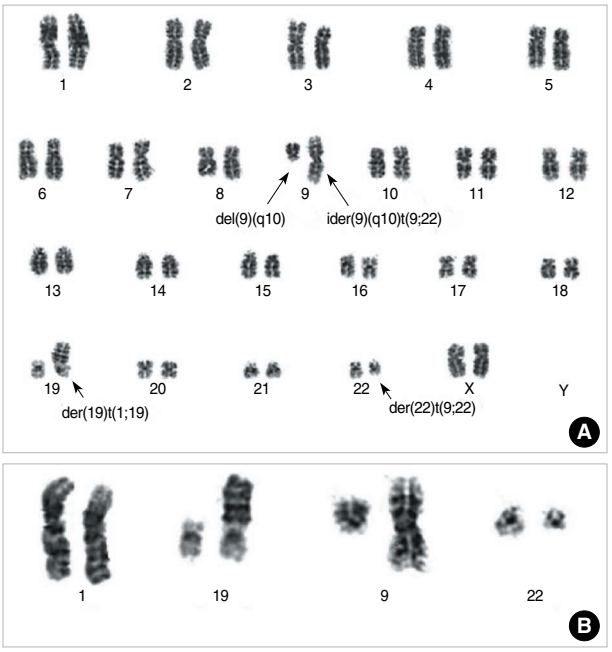

Fig. 3. The representative full karyogram (A) and partial karyogram (B) showed 46,XX,ider(9)(q10)t(9;22)(q34;q11.2),del(9)(q10),der(19)t(1;19)(q23;p13.3),der(22)t(9;22).

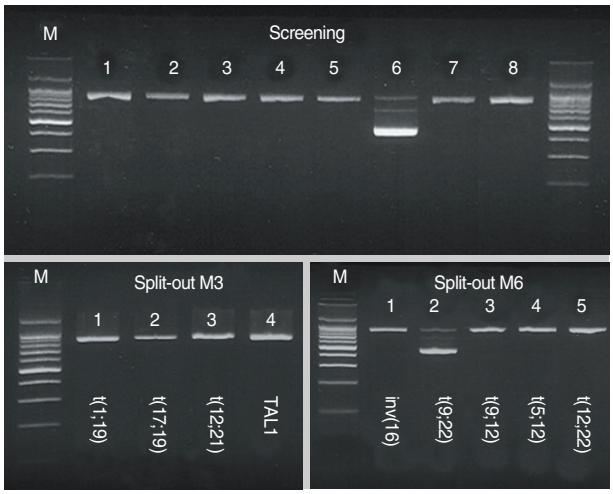

Fig. 5. Multiplex nested reverse transcriptase PCR using a HemaVision kit. The 911-bp bands in each lane represent internal controls. The 472-bp band seen in lane 6 of the screening PCR and lane 2 of the split-out M6 PCR represents the *BCR/ABL1* b3a2 transcript. The *TCF3/PBX1* transcript is not seen in either the screening or the split-out M3 PCR.

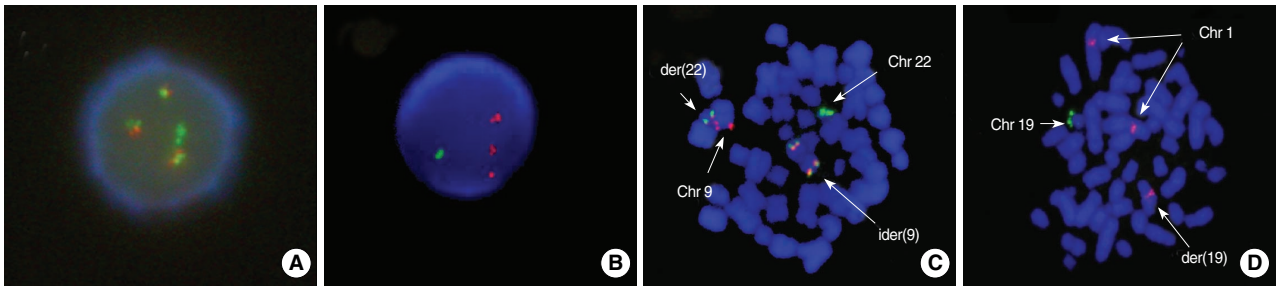

Fig. 4. (A) FISH using the *BCR/ABL1* dual color dual fusion translocation probe at relapse. One green signal represents the normal chromosome 22, and 3 fusion signals are seen. Loss of red signal is consistent with deletion of the long arm of normal chromosome 9. (B) FISH using the *TCF3/PBX1* dual color dual fusion translocation probe at relapse showed 1 green and 3 red signals with no fusion signal. (C) FISH using the *BCR/ABL1* dual color dual fusion translocation probe at initial diagnosis. Fusion signals are demonstrated on der(22) and both arms of ider(9). (D) FISH using the *TCF3/PBX1* dual color dual fusion translocation probe at initial diagnosis. Fusion signal is not observed on der(19).

veloped invasive aspergillosis. She withdrew from follow-up after October 2009.

DISCUSSION

The isochromosome of the long arm of derivative chromosome 9 from t(9;22) with a deletion of 9p, ider(9)(q10)t(9;22) is very rare. Only 15 cases have been reported to date; 5 cases with CML in the blast phase and 10 cases with ALL. All of the previously reported cases with ider(9)(q10)t(9;22) were B-ALL or lymphoid blast phase of CML, except for 1 case of CML in the blast phase and 1 case of ALL that were not described as blast lineage. Thus, it appears that this abnormality is specific to precursor B lymphoid malignancies (Table 1) [2-14]. This abnormality has not been reported in the chronic phase of CML and most likely evolved from a preexistent standard t(9;22). Therefore, it is probably associated with the progression of CML [5, 10, 11]. The formation of ider(9)(q10)t(9;22) leads to the loss of 9p, whereas the long arm of der(9)t(9;22) is duplicated. Because of the limited number of cases and different therapeutic approaches used, the prognosis of B-ALL implicated by ider(9)(q10)t(9;22) is difficult to assess, but it is generally accepted that the 9p deletion is associated with poor outcome [5, 7, 17]. Deletion or unbalanced translocations of 9p have been reported in 7-13% of patients with ALL. The chromosome region commonly deleted is 9p21-22; this leads to loss of the genes encoding methylthioadenosine phosphorylase (an important enzyme in purine metabolism), tumor suppressors such as $p15^{INK4b}$/$p16^{INK4a}$/$p14^{ARF}$, and cyclin-dependent kinase inhibitor enzymes. These genes may be involved in tumorigenesis and/or chemosensitivity [18, 19]. Conversely, genes located on the long arm of der(9)t(9;22) are overexpressed. The enhanced tyrosine kinase activity of *BCR-ABL1* causes the constitutive activation of several signal transduction pathways and acquisition of an additional *BCR-ABL1* fusion gene, such as on an extra Philadelphia chromosome, is associated with disease progression [1]. However, the clinical significance of an additional *ABL-BCR1* fusion gene due to ider(9)(q10)t(9;22) is not yet clear. In addition, deletion of the long arm of the normal chromosome 9, which includes the *ABL1* gene, was noted as clonal evolution at relapse. Several genes, such as *SET*, *ABL1* and *NUP214*, within the 9q34 region have been implicated in leukemogenesis [2, 20]. One of the most common chromosomal abnormalities in B-cell precursor ALL is t(1;

Table 1. Clinical and cytogenetic findings of the reported cases of ider(9)(q10)t(9;22)(q34;q11.2)

Case No.	Gender/ Age	Diagnosis	Karyotype	Ref. No.
1	F/63	c-ALL	46,XX,idic(9)(p13)t(9;22)(q34;q11.2),der(22)t(9;22)/46,XX	[3]
2	M/16	ALL	46,XY, ider(9)(q10)t(9;22)(q34;q11),der(22)idic(p13)t(9;22)	[4]
3	M/30	c-ALL	46,XY,add(1)(p36),ider(9)(q10)t(9;22)(q34;q11),add(12)(p13),add(16)(p13), der(22)t(9;22)[8] /46,XY[2]	[5]
4	M/53	c-ALL	46,XY,t(9;22)(q34;q11)[4]/45,XY,-7,i(8)(q10),ider(9)(q10)t(9;22),der(22)t(9;22)[32]/46,XY[5]	[6]
5	M/31	c-ALL	46,XY,ider(9)(q10)t(9;22)(q34;q11),der(22)t(9;22)[23]/46,XY[4]	
6	ND	ALL (B)	46,XX,ider(9)(q10)t(9;22)(q34;q11),der(22)t(9;22)	[7]
7	ND	ALL (B)	47,XY,+8, ider(9)(q10)t(9;22)(q34;q11),der(22)t(9;22)/48,idem,+mar	
8	M/12	c-ALL	46,XY,ider(9)(q10)t(9;22)(q34;q11),der(22)t(9;22)[19]/48,XY,t(9;22),+21,+der(22)t(9;22)[1]	[8]
9	F/3	preB-ALL	46,XX,t(9;22)(q34;q11)[3]/47,idem,+X[6]/46,XX, ider(9)(q10)t(9;22),der(22)t(9;22)[4] /46,XX[12]	[9]
10	F/26	ALL (B)	46,XX,ider(9)(q10)t(9;22)(q34;q11.2),der(22)t(9;22)[10]/46,XX[10]	[10]
11	F/26	CML, lymphoid BP	46,XX,t(9;22)(q34;q11)[9]/45,XX,-7,ider(9)(q10)t(9;22),der(22)t(9;22)[3]/46,XX[8]	[11]
12	M/34	CML, BP	46,XY,t(9;22)(q34;q11)[2]/46,XY,ider(9)(q10)t(9;22),der(22)t(9;22)[5]	[12]
13	F/58	CML, B lymphoid BP	46,XX,t(9;22)(q34;q11)/45,XX,-7,ider(9)(q10)t(9;22),der(22)t(9;22)/46,XX	[13]
14	M/30	CML, B lymphoid BP	46,XY,t(9;22)(q34;q11)[6]/46,XY,ider(9)(q10)t(9;22),der(22)t(9;22)[9]/ 47,XY,+8,ider(9)(q10)t(9;22),der(22)t(9;22)[5]	[5]
15	M/42	CML, B lymphoid BP	46,XY,t(9;22)(q34;q11.2)[12]/46,XY,ider(9)(q10)t(9;22),der(22)t(9;22)[10]/ 45,XY,-9,der(22)t(9;22)[3]	[14]
16	F/45	ALL (B)	46,XX,ider(9)(q10)t(9;22)(q34;q11.2),del(9)(q10),der(19)t(1;19)(q23;p13.3),der(22)t(9;22)[20]	This case

Abbreviations: Ref, reference; F, female; M, male; c-ALL, common ALL; ALL (B), B-lineage ALL; BP, blast phase.

19)(q23;p13), and it usually gives rise to the *TCF3-PBX1* fusion gene, which has an oncogenic role as a transcriptional activator [1]. While *TCF3* (on 19p13) is fused to *PBX1* (on 1q23) in most cases of ALL with a t(1;19), 5-12% of cases have translocations that appear cytogenetically identical, but do not affect *TCF3* or *PBX1* [21, 22]. FISH and multiplex nested RT-PCR did not reveal *TCF3-PBX1* fusion in this patient, but der(19)t(1;19) was identified using conventional cytogenetic analysis. This is the first reported case of ALL with *TCF3-PBX1* negative t(1;19) in Korea. Previous studies showed that B-ALL with *TCF3-PBX1* negative t(1;19) did not demonstrate the expected phenotypes of *TCF3-PBX1* positive ALL, such as the cIg(+) pre-B phenotype, and usually presented with the cIg(-) early pre-B phenotype and hyperploidy. Initially, t(1;19) was associated with a poor prognosis, but modern intensified treatment protocols have improved the outcome of these patients [1]. Although it remains unclear whether the prognosis of *TCF3-PBX1* negative t(1;19) differs from that of *TCF3-PBX1* positive t(1;19), cIg(-) early pre-B ALLs with t(1;19) and hyperdiploid karyotypes have been reported to have a more favorable prognosis; thus, it appears that *TCF3-PBX1* negative t(1;19) is associated with a more favorable outcome than *TCF3-PBX1* positive cases [23]. The mechanism responsible for the formation of *TCF3-PBX1* negative t(1;19) is still unknown. One possibility is that other genes are rearranged by cytogenetically indistinguishable translocations. In fact, involvement of the *MEF2D* gene (1q12-q23) and the *DAZAP1* gene (19p13.3) was recently identified in B-ALL with t(1;19) [21]. However, *MEF2D* was not included in the FISH probe that we used, and *DAZAP1* is more telomeric than *TCF3;* the FISH results for this case were not consistent with *MEF2D* or *DAZAP* involvement. Although the clinical significance and molecular characteristics of *TCF3-PBX1* negative t(1;19) are unknown, it appears to be distinct from *TCF3-PBX1* positive t(1;19). A molecular method is needed to confirm cases of t(1;19). Both t(9;22) and t(1;19) are common, nonrandom chromosomal rearrangements in B-ALL. However, the concurrent occurrence of both abnormalities is very rare. In our patient, der(19) was identified by FISH at the initial diagnosis in a proportion similar to that of ider(9); this finding is consistent with concurrent occurrence rather than clonal evolution. A literature and database review revealed only 3 reported cases of childhood ALL with both t(1;19) and t(9;22) [2, 24]. This study is the first report of the concurrent occurrence of ider(9)(q10)t(9;22) and *TCF3-PBX1* negative t(1;19). In 2 previously reported patients who relapsed, the t(1;19)-containing clones disappeared, but t(9;22) persisted. The 2 patients who received an epipodophyllotoxin developed secondary myeloid leukemia with entirely new cytogenetic findings [24]. In our case, the patient relapsed after a 9-month remission, and the disease persisted despite intensive chemotherapy and imatinib therapy. Although both the previously reported cases and our case had poor outcomes, because of the small number of cases, it is not clear whether the additional t(1;19) increased the severity of ALL with t(9;22). According to the WHO classification, t(9;22) may be associated with other genetic abnormalities, and it is generally accepted that the clinical features are governed by the presence of t(9;22) [1]. Both ider(9)(q10)t(9;22) and *TCF3-PBX1* negative t(1;19) are rare cytogenetic abnormalities of B-ALL, and a larger study and more case reports are needed to determine the prognostic significance of ider(9)(q10)t(9;22) and *TCF3-PBX1* negative t(1;19).

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