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)

Soon Il Jung, M.D.¹, Hee Soon Cho, M.D.¹, Chae Hoon Lee, M.D.¹, and Bo-Chan Jung, M.D.¹

Department of Laboratory Medicine¹, Yeungnam University College of Medicine, Daegu; Department of Laboratory Medicine², Gumi CHA General Hospital, Pochon CHA University College of Medicine, Gumi, Korea

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)(q22) is a rare variant of t(9;22) with a deletion of the short arm of chromosome 9. Fifteen cases of ider(9)(q10)(q22) 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)(q22) 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)
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 3.8×10^9/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, CD3, 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) (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

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**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-
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 p15INK4b/p16INK4a/p14ARF, 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>
<thead>
<tr>
<th>Case</th>
<th>Gender/ Age</th>
<th>Diagnosis</th>
<th>Karyotype</th>
<th>Ref. No.</th>
</tr>
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<tbody>
<tr>
<td>1 F/63</td>
<td>c-ALL</td>
<td>46,XX,ider(9)(p13)(9;22)(q34;9q11.2),der(22)(9;22)/46,XX</td>
<td>[3]</td>
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<tr>
<td>2 M/16</td>
<td>ALL</td>
<td>46,XY,ider(9)(q10)(9;22)(q34,q11),der(22)(p13)(9;22)</td>
<td>[4]</td>
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</tr>
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<td>3 M/30</td>
<td>c-ALL</td>
<td>46,XY,add(1)(p36),ider(9)(q10)(9;22)(q34;q11),add(12)(p13),add(16)(p13),der(22)(9;22)[8]/46,XY</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>4 M/53</td>
<td>c-ALL</td>
<td>46,XY,i(9;22)(q34;q11)[4]/45,XY,-7,i(8)(q10),ider(9)(q10)(9;22),der(22)(9;22)[32]/46,XY</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>5 M/31</td>
<td>c-ALL</td>
<td>46,XY,ider(9)(q10)(9;22)(q34,q11),der(22)(9;22)[23]/46,XY</td>
<td>[4]</td>
<td></td>
</tr>
<tr>
<td>6 ND</td>
<td>ALL (B)</td>
<td>46,XX,ider(9)(q10)(9;22)(q34,q11),der(22)(9;22)</td>
<td>[7]</td>
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</tr>
<tr>
<td>7 ND</td>
<td>ALL (B)</td>
<td>47,XY,+8,ider(9)(q10)(9;22)(q34,q11),der(22)(9;22)/48,idem,+mar</td>
<td>[8]</td>
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<tr>
<td>8 M/12</td>
<td>c-ALL</td>
<td>46,XY,ider(9)(q10)(9;22)(q34,q11),der(22)(9;22)[19]/48,XY,i(9;22),+21,+der(22)(9;22)[1]</td>
<td>[9]</td>
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<tr>
<td>9 F/3</td>
<td>preB-ALL</td>
<td>46,XX,i(9;22)(q34;q11)[3]/47,ider(9)(q10)(9;22),der(22)(9;22)[4]/46,XX</td>
<td>[9]</td>
<td></td>
</tr>
<tr>
<td>10 F/26</td>
<td>ALL (B)</td>
<td>46,XX,ider(9)(q10)(9;22)(q34,q11),der(22)(9;22)[10]/46,XX</td>
<td>[10]</td>
<td></td>
</tr>
<tr>
<td>11 F/26</td>
<td>CML, lymphoid BP</td>
<td>46,XY,i(9;22)(q34;q11)[9]/45,XY,-7,ider(9)(q10)(9;22),der(22)(9;22)[3]/46,XX</td>
<td>[11]</td>
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<td>12 M/34</td>
<td>CML, BP</td>
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<td>[13]</td>
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<td>46,XY,i(9;22)(q34;q11)[6]/46,XY,i(9)(q10)(9;22),der(22)(9;22)[9]/47,XY,ider(9)(q10)(9;22),der(22)(9;22)[5]</td>
<td>[14]</td>
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<td>[15]</td>
<td></td>
</tr>
<tr>
<td>16 F/45</td>
<td>ALL (B)</td>
<td>46,XX,ider(9)(q10)(9;22)(q34,q11.2),del(9)(q10),der(19)(1;19)(q23;p13.3),der(22)(9;22)[20]</td>
<td>[16]</td>
<td></td>
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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 clg(+) pre–B phenotype, and usually presented with the clg(−) 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), clg(−) 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).

REFERENCES


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