

CLINICAL STUDY

The variant translocation of ABL1 Gene t(2;9)(q21;q34) in a childhood T-cell acute lymphoblastic leukemia

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Abstract: We present the case of the childhood ALL that was identified by the translocation of the ABL1 gene to the q21 band of chromosome 2 without t(9;22)(q34;q11) translocation. The observation of a poor clinical course of the case may contribute to explanation of the action of t(9;22)(q34;q11) translocation, of which poor prognostic action is known on ALL's, in terms of ABL1 gene, independent of the BCR gene. On the other hand, the prognostic significance of this variant ABL1 translocation detection, which is very rarely observed, will cast a light on future cases (Tab. 1, Fig. 1, Ref. 11). Full Text in free PDF www.bmj.sk.

Keywords: ABL1 gene translocation, T cell ALL.

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, which accounts for one third of all pediatric cancers. Some numerical and structural chromosomal abnormalities, including the translocations t(9;22)(q34;q11), t(12;21)(p13;q22), rearrangements of the MLL gene, hyperdiploidy and hypodiploidy are known as prognostic factors in the childhood ALL. Hyperdiploidy is defined as the gain of one or more chromosomes in a nonrandom fashion. In older children with B-precursor ALL, the two most common chromosomal abnormalities are high hyperdiploid (51–65 chromosomes or DNA index ≥ 1.16) and the t(12;21)(p13;q22) translocation, each observed in approximately one-third of cases. Whereas t(9;22)(q34;q11), rearrangements of the MLL gene translocations and hypodiploidy are well known to be poor prognostic factors, the translocation of t(12;21)(p13;q22) and hyperdiploidy is speculatively a good prognostic marker(1–5). The Abelson tyrosine kinase gene (ABL1) is located on chromosomal band 9q34. The main fusion partner of ABL1 gene is BCR (Breakpoint Cluster Region), involved in the t(9;22)(q34;q11), present in more than 95 % of patients with chronic myeloid leukemia, in 20 % of adults with pre-B ALL and in 2–3 % of childhood ALL (6).

Furthermore, it is known that the ABL1 gene rarely translocates to chromosomes 1q24, 14q32 and 10q22.3 (6–8). In generally, some chromosomal abnormalities are not found at diagnosis, but may develop after treatment. We report a very rare variant of ABL1 translocation involved in a t(2;9)(q21;q34), which may cast a light on prognosis of similar cases in future.

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Case report

A two-year-old girl was hospitalized at our department of pediatric hematology in May 2007 with a complaint of a nodule in the neck. During the physical examination, multiple lymphadenopathy, hepatosplenomegaly and skin related symptoms were detected. Hematological data were as follows: hemoglobin level 8 g/dl, white blood cell level $324 \times 10^9/l$ with 100 % blast cells and platelets at a level of $57 \times 10^9/l$. Bone marrow aspirate showed hypercellularity with 100 % of lymphoblasts. Immunophenotyping showed results corresponding to T-ALL. The ALL BFM-95 treatment protocol was started. On day 8, steroid response was poor. The bone marrow examination was performed on day 15 and concluded as hypocellular. On day 30 of the treatment, the leukocyte level running earlier at a range of $3 \times 10^9/l$ – $5 \times 10^9/l$ was identified to rise up to a level of $30 \times 10^9/l$, the smear had a 90 % blast. While the patient went through HR1 BLOK and IDA-FLAG treatment regimes, she did not enter remission and was lost in the third month of treatment due to primary disease progression and sepsis.

The conventional G-Banded cytogenetic analysis was performed on bone marrow cells after 48 and 72 hours in cultures without mitogenic stimulations. The karyotype was described according to ISCN(2005). Although the karyotype was found to be normal during diagnosis, a 46,XX,t(2;9)(q21;q34),del(11)(p15)[15]/46,XX[5] karyotype was found in bone marrow cells from the 30th day of treatment onwards (Fig. 1A).

Fluorescence In Situ Hybridization (FISH) was performed using the LSI BCR/ABL ES dual color translocation probe described by the manufacturer (Vysis). On the 30th day of treatment, using an LSI BCR/ABL ES dual color translocation probe, three red signals were seen, one on the normal chromosome 9, one on the der(9) and another on the der(2), signing the t(2;9)(q21;q34) with involvement of the ABL1 gene (Fig. 1B).

Tab. 1. Clinic and laboratory features of the childhood ALL with rare variant translocations of ABL1 gene.

Case	Age	Gender	Leucocyte count at diagnosis	Leukemia type	Translocations	Prognosis
Case 1 (7)	11 y	Male	104x10 ⁹ /L	Pre-B ALL	t(1;9)(q24;q34)	Complete remission was achieved and the patient received a bone marrow transplantation
Case 2 (6)	16 y	Female	455x10 ⁹ /L	T-ALL	t(9;14)(q34;q32)	Remission 15 months after diagnosis
Case 3 (8)	18 m	Female	neutrophils 0 GI ⁻¹	Pre-B ALL	t(9;10)(q34;q22.3)	Remission
Our Case	2 y	Female	324x10 ⁹ /L	T-ALL	t(2;9)(q21;q34)	Exitus three months after diagnosis

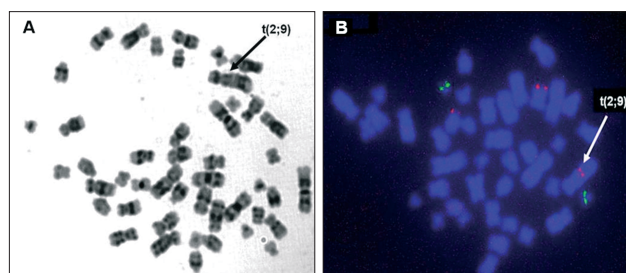


Fig. 1. A: G-banded karyotype showing the t(2;9)(q21;q34) translocation (arrow). **B:** FISH using LSI BCR/ABL ES Dual Color Translocation Probe revealed two normal green signals (22q11), three red signals (one on the normal chromosome 9, one on the der(9) and another on the der(2) (arrow)).

Discussion

Structural variations in leukemia are generally observed as deletion, inversion and amplification while the majority consists of translocations. Most of these variations lead to deformations in genes that manage cell differentiation and control cell growth, which play a role in hematopoiesis. It is claimed that translocations manage this in two particular ways. First, abnormal oncogenic expression, and second, the structurally and functionally abnormal protein coding of the new fusion gene (9). The most frequently observed translocations in the childhood ALL are t(12;21)(p13;q22) at a rate of 20–25 %; t(9;22)(q34;q11) at a rate of 2 %; and MLL gene rearrangement at a rate of 2–4 % (1, 2). It is stated that in these translocations t(12;21)(p13;q22) is related to good prognosis while t(9;22)(q34;q11) and MLL gene rearrangement are related to poor prognosis (10, 11). Except these classic translocations, there are some rare translocations, which might affect prognosis in literature (6–8). Some acute leukemia cases were reported with translocation other than t(9;22)(q34;q11), such as t(1;9)(q24;q34), t(9;14)(q34;q32), t(9;10)(q34;q22.3) variant translocations. These cases are summarized in the Table 1. In a case with an 11 year old boy with pre-B ALL, having t(1;9)(q24;q34) translocation, relapse was observed and bone marrow transplantation was conducted later (7). On the other hand, in a case with a 16 year old girl with T-ALL having t(9;14)(q34;q32) translocation, a high level of leukocytes were detected, however she entered remission 15 months after diagnosis (6). Notwithstanding this, in the case of an 18 month girl with B-ALL having t(9;10)(q34;q22.3), early remission was recorded (8). As described in literature, it is recorded that different ALL subtypes of variant translocations of ABL gene (T-ALL, preB-ALL and B-ALL) are observed at different ages and cause different levels of leukocyte counts. Our case is a two years old child with T immune

phenotype. Also, the leukocyte level was high not only during the diagnosis stage but also in the instant when translocation was identified. In literature, while one case relapsed, the other two entered remission. Variant translocations of ABL gene were identified during the diagnosis stage. However, our case was refractory to treatment and was lost with disease progression and sepsis in the third month. In the light of this information, it was observed that translocation of ABL gene to other chromosomes besides chromosome 22 may affect prognosis. Another characteristic feature in our patient is that t(2;9)(q21;q34) translocation was identified after treatment on day 30.

To conclude, it is considered that the case reported here will contribute to literature, both since a different translocation related to malignant prognostic action in ALL's is demonstrated and since this supports the idea that the malignant prognostic action of t(9;22)(q34;q11) translocation is related to the variations of ABL1 gene instead of the BCR gene variations. On the other hand, the fact that a translocation was detected on day 30 while no translocation was detected during the diagnosis stage supports the assertion that consistent genetic analysis is required in such cases.

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