A Rare Case of Acute Lymphoblastic Leukemia with t(12;17)(p13;q21)

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INTRODUCTION

Since the third International Workshop on Chromosomes in Leukemia in 1980, cytogenetic abnormalities have been established to be very important for the prognosis of ALL [1]. Abnormal karyotypes have been reported in up to 80% of children and 70% of adults with ALL [2]. Abnormalities in the short arm of chromosome 12 are common in childhood ALL and t(12;21)(p13;q22) are well-known chromosomal abnormalities. However, t(12;17)(p13;q21) is a rare cytogenetic abnormality in patients with ALL. To the best of our knowledge, approximately 20 cases of this abnormality have been reported in the literature [1, 3–9]. In this study, we report presumably the first case of this abnormality in Korea, thereby facilitating the delineation of a distinct subtype of ALL.

CASE REPORT

A 57-yr-old woman was admitted to our hospital for the treatment of pancytopenia. On admission, her medical history and physical examination findings were unremarkable. Peripheral blood examination showed the following findings: Hb level, 8.8 g/dL; leukocyte count, 3,120/µL; and platelet count, 37,000/µL with 2% neutrophils, 39% lymphocytes, 55% blasts, and 5 nucleated red cells per hundred of white blood cells (Fig. 1A). On the basis of these findings, we suspected acute leukemia...
The bone marrow was markedly hypercellular with nearly 90–100% cellularity, and about 82.4% of all nucleated cells were blasts. The blasts were medium-sized and had moderate amounts of cytoplasm with many vacuoles and indistinct nucleoli (Fig. 1B). Cytochemical staining showed that the cells were positive for specific esterases, with dot-like positivity for periodic acid–Schiff, and they were negative for myeloperoxidase, Sudan black B, and non–specific esterases. Immunophenotyping showed positivity for CD19 (49.1%), CD33 (81.6%), and CD34 (58.8%) and negativity for CD2 (6.91%), CD3 (3.66%), CD5 (6.79%), CD7 (0.41%), CD33 (1.04%), Tdt (0.30%), CD10 (0.01%), CD20 (1.48%), HLA–DR (0.85%), and CD13 (1.76%).

Fig. 1. Peripheral blood smear (A) showing blasts. Bone marrow smear (B) revealed many medium-sized lymphoblasts (about 82.4% of all nucleated cells) with moderate amount of cytoplasm, many vacuoles, and indistinct nucleoli (Wright-Giemsa stain, ×1,000).

Fig. 2. Giemsa-banded karyotype showing 46,X,-X,+8,der(12)t(12;17)(p13;q21),t(12;17)(p13;q21) (arrows).
Cytogenetic studies on the bone marrow cells were performed by incubating the cells in an unstimulated culture media for 24 hr. The chromosomes were analyzed using G-banding, and the karyotype was described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2009 [10]. Cytogenetic analysis of the bone marrow showed the following complex karyotype, including a reciprocal translocation between the short arm of chromosome 12 and the long arm of chromosome 17, t(12;17)(p13;q21), in 16 out of 21 cells: 46,X,-X,+8,der(12)t(12;17)(p13;q21),t(12;17)(p13;q21)[16]/46,XX [5] (Fig. 2). FISH for the detection of TEL/AML1, MLL, PML/RARA, and BCR/ABL1 rearrangement showed normal results. The patient was diagnosed with precursor B-ALL. She was treated with hyper-CVAD chemotherapy comprising cyclophosphamide, vincristine, adriamycin, and dexamethasone, and this treatment resulted in complete remission.

We also performed array comparative genomic hybridization (CGH) analysis by using DNA extracted from the marrow and the SignatureChip array (Signature Genomic Laboratories, Spokane, WA, USA). Microarray analysis of 1,543 loci using 4,685 bacterial artificial chromosome clones revealed 5 chromosomal abnormalities in

Fig. 3. The results of array comparative genomic hybridization were consistent with cytogenetic findings. The pink line represents the patient-to-control fluorescence intensity ratios, whereas the dark blue line represents dye-reversed control-to-patient fluorescence ratios. The microarray analysis revealed that the patient had 5 chromosomal abnormalities. The second abnormality is an approximately 6.6-Mb terminal deletion of the short arm of chromosome 12 at 12p13.33-12p13.31. The fourth abnormality is an approximately 47.4-Mb terminal duplication of the long arm of chromosome 17 at 17q12-17q25.3.
the patient’s DNA, a finding consistent with the cytogenetic findings (Fig. 3): the abnormalities are represented as arr Xp22.33q28(262,578–154,566,678)×1, 8p23.3q24.3 (345,060–146,236,298)×3, 12p13.33p13.31(74,345–6,696,823)×1, 17q11.2(266,415,260–26,627,398)×1, and 17q12q25.33q21,836–78,654,742)×3.

DISCUSSION

Translocation (12;17) has been reported mainly in children and young adults with ALL and AML [1, 3–9]. The assignment of translocation breakpoint has been reported to be slightly different among different studies, but some or all of those cases are likely to represent the same translocation because breakpoint assignment is quite subjective [5].

Krance et al. [5] reported 5 patients with early pre-B ALL and t(12;17)(p13;11). However, 2 patients expressed the myeloid–associated antigen CD33, and the CD10 antigen was absent or present at low levels in all 5 patients. Complete remission was achieved in all 5 patients. During subsequent therapy, 2 patients relapsed and 3 remained in continuous remission for more than 20 months. Another study reported that 2 cases of t(12;17) in ALL had a precursor–B immunophenotype and were CD33 positive and CD10 negative. These patients also achieved complete remission and remained in that condition [8]. Our findings were also similar to those reported above: precursor B–ALL, positivity for CD33, negativity for CD10, and favorable prognosis.

Some reports suggest that the expression of myeloid antigen on ALL leukemic cells has an adverse prognostic influence. However, other researchers have argued that the coexpression of myeloid–associated antigens in the cases of B–cell progenitor ALL has no prognostic significance in childhood ALL [5]. Lack of CD10 expression has been associated with adverse biologic and clinical features [8]. Further, low levels of CD10 expression have been reported to be associated with a higher rate of induction failure, but they have no other prognostic significance in B–cell lineage ALL [5]. The t(12;17) abnormality has been reported to be associated with a poor prognosis [4, 6]; however, a favorable prognosis was observed in some cases, including ours. Currently, not many cases have been reported, and therefore, a robust relationship between the prognosis and the expressions of CD33 and CD10 cannot be determined.

The characteristic feature of our case was that it had t(12;17) as well as an additional der(12)t(12;17) chromosomal abnormality, thereby resulting in 3 copies of 17q. To our knowledge, this is the first report of 17q trisomy in a patient with ALL. The role of 17q trisomy in this entity remains to be investigated.

A well-established association exists between 12p abnormalities in ALL and rearrangement of the TEL transcription factor [8]. In our study, FISH excluded involvement of the TEL locus in t(12;17), thereby indicating that the rearrangement of TEL in this translocation does not play a role in the malignant transformation. The mechanism by which TEL–negative rearrangements contribute to disease pathogenesis is currently unknown. A recent molecular study of 8 patients showed for the first time that the CIZ gene was involved in leukemia [11]. Among the 8 patients, 6 (75.0%) had the t(12;17)(p13;11) abnormality. In acute leukemia, the transcription factor gene CIZ/NMP4 is recurrently rearranged through fusion with either EWSR1 or TAF15. TET–CIZ fusions could provide an interesting model to investigate alternative oncogenic pathways for t(12;17). CIZ rearrangements characterize a specific hematological/genetic ALL subset with early–B phenotype, myeloid marker expression, no bulky disease, and onset in young adults and children [12]. Thus, detailed genomic analysis of the t(12;17) abnormality is required to identify the oncogenic mechanism responsible for t(12;17)–positive ALL.

In summary, t(12;17)(p13;11) is a rare chromosomal abnormality of ALL and is associated with the expression of myeloid antigens. In this study, we report a case of ALL with the chromosomal abnormality t(12;17) (p13;11), which was identified by conventional cytogenetics and array CGH. Our case indicates that cytogenetic and molecular studies are important for the accu-
rate diagnosis of this unusual clonal abnormality and further analyses of such cases are required to accurately define this rare disease entity.

**REFERENCES**


