

A case of acute lymphoblastic leukemia with additional chromosomes X and 5 associated with a Philadelphia chromosome in the bone marrow

Kemik iliğinde ekstra kromozom 5 ve X'e ilave Philadelphia kromozomu içeren akut lenfoblastik lösemi olgusu

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Abstract

We report herein a very rare case of acute lymphoblastic leukemia having a chromosomal constitution of 48,XY,+X,+5,t(9;22)(q34;q11) in the bone marrow. A patient with additional chromosomes X and 5 with a Philadelphia chromosome has not been reported previously. However, no abnormal karyotype was obtained from the lymphocytes in our patient, and he did not have the characteristics of Klinefelter syndrome. He achieved a complete remission with IDA-FLAG and dasatinib therapy. The mechanism of trisomy 5 or any other chromosomal aneuploidy in the pathogenesis of leukemogenesis remains unclear. Further studies involving the genes affected by this karyotype and their products may lead to strategies to further increase the understanding of drug-resistant acute lymphoblastic leukemia and may represent the next frontier in the targeted therapy of those patients. (*Turk J Hematol 2010; 27: 299-302*)

Key words: ALL, X chromosome, chromosome 5, Philadelphia chromosome

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Özet

Bu makalede, kemik iliğinde çok nadir bir kromozom yapısı olan 48,XY,+X,+5,t(9;22)(q34;q11)'e sahip bir olgu sunulmaktadır. Ekstra kromozom 5 ve X'e ilave olarak Philadelphia kromozomunu taşıyan bir olguya literatürde rastlanmamıştır. Hastamızın lenfositlerden elde edilen karyotipi normal olarak değerlendirilmiş olup, Klinefelter Sendromu kliniği bulunmamaktaydı. IDA-FLAG tedavisi sonucunda tam remisyona sağlandı. Trizomi 5 veya diğer kromozomal anöloidilerin lökomogenez üzerindeki rolü net değildir. Karyotipte saptanmış olan bölgelerdeki genler ve ürünlerinin yapılacak çalışmalarla incelenmesi, ilaca dirençli akut lenfoblastik lösemiye anlamamızda ve bu hastaların hedefe özgün tedavi seçeneklerinde yardımcı olabilecektir. (*Turk J Hematol 2010; 27: 299-302*)

Anahtar kelimeler: ALL, X kromozomu, kromozom 5, Philadelphia kromozomu

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Introduction

Chromosomal abnormalities have been reported in 60-85% of patients with acute lymphoblastic leukemia (ALL) [1]. Cytogenetic aberrations are not only important in the evaluation of prognosis but are also useful in classifying patients into risk groups [2]. Numerical chromosomal changes such as hypodiploidy are associated with poor outcome, while hyperdiploidy is shown to be associated with a better prognosis [3]. Even though aneuploidies usually occur in autosomal chromosomes, sex chromosome aneuploidies may also be associated with hyperdiploidy in ALL. Trisomy 5 and sex chromosome aneuploidies in high-hyperdiploid karyotypes have been found in 20% of ALL patients, which revealed poor prognosis [4]. Compared with all chromosomal abnormalities, less is known about patients with trisomies as a sole numerical chromosomal abnormality. Since single trisomies are extremely rare, with an incidence of 1%, their prognostic value and relevant clinical features have not been established in ALL patients [5]. Trisomy 5 is a very rare chromosomal abnormality, with only few cases in the literature, and it is shown to be associated with other chromosomal abnormalities [6]. For instance, an additional X chromosome is a rare finding observed in the hematological malignancies [7]. Besides numerical abnormalities, Philadelphia (Ph) chromosome is the most common cytogenetic abnormality, occurring in almost 25% of ALL adults [8]. Here, we present an unusual ALL case with a full karyotype showing an additional X chromosome, chromosome 5 and a Ph chromosome in the bone marrow, and we discuss the outcomes and the management of these rare chromosomal abnormalities.

Case Report

An 18-year-old male patient was referred to our hospital with fatigue, weakness and weight loss. On physical examination, massive splenomegaly was recorded (total vertical length: 180 mm). The complete blood count (CBC) showed white blood cell (WBC) count 30000/L, hemoglobin (Hb) 10 g/dl, hematocrit (Hct) 30%, and platelet (PLT) count 23000/mm³. Peripheral blood smear (PS) showed leukocytosis and the presence of 90% myeloblastic cells, which were peroxidase- and periodic acid-Schiff-(PAS)-negative. Biochemical parameters

were within normal limits except lactate dehydrogenase (LDH) of 788 U/L. Bone marrow aspiration and biopsy specimen were consistent with the diagnosis of B-cell ALL showing 90% myeloblastic cells infiltration. Hoelzer protocol phase I treatment was started [9]. At diagnosis, the karyotype obtained from the bone marrow revealed trisomies of chromosomes X and 5 with a Ph chromosome and was reported as 48,XXY,+X,+5,t(9;22)(q34;q11) (Figure 1). In the meantime, molecular BCR/ABL fusion gene was detected by molecular analysis. Regarding the Ph positivity, 400 mg/day imatinib-mesylate combination was added to his chemotherapy regimen. After continuing the treatment for three months, he was hospitalized due to deterioration in his condition and bone pain. Bone marrow aspiration showed more than 90% peroxidase- and PAS-negative blastic infiltration. Since a very high level of BCR/ABL fusion gene expression was detected by reverse transcription-polymerase chain reaction (RT-PCR), he was considered to be relapsed Ph (+) ALL, and IDA-FLAG protocol (idarubicin 12 mg/m²/day 3 days, fludarabine 30 mg/m²/day 5 days, AraC 2 g/m² 5 days) was started. At the time of relapse, cytogenetic analysis from his bone marrow aspiration material showed a full karyotype of 48,XXY,+X,+5,t(9;22)(q34;q11), the same as at the time of diagnosis. However, physical examination was not consistent with the features of Klinefelter syndrome, and the cytogenetic evaluation of his peripheral blood showed a normal karyotype. Failure to achieve complete remission led us to add another tyrosine kinase inhibitor, dasatinib (70 mg/day), to the treatment protocol. After one month of the treatment, his bone marrow aspiration showed 4% blastic infiltration with normal immunohistochemical staining and flow cytometry. During follow-up, cytogenetic analysis of bone marrow aspiration material revealed a normal karyotype, indicating a complete cytogenetic remission. He was considered to be in remission, and he is still under IDA-FLAG and dasatinib treatment. Written informed consent was obtained from the patient's family.

Discussion

Trisomy 5 usually occurs in a high-hyperdiploid karyotype or secondary to structural abnormalities, in particular t(9;22)(q34;q11.2), t(12;21)(p13;q22) and t(1;19)(q23;p13). Those conditions are more

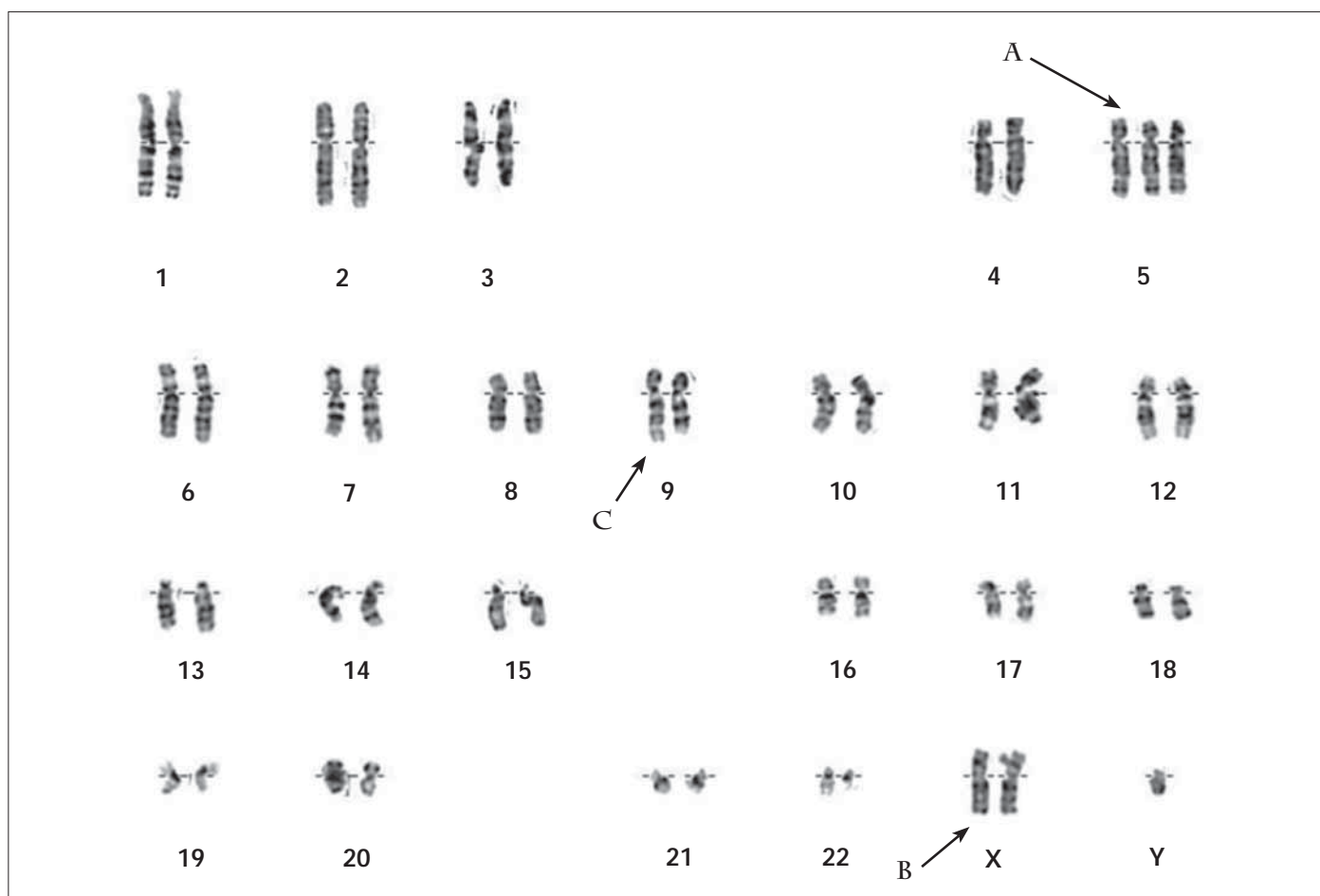


Figure 1. The karyotype of the patient obtained from bone marrow, showing trisomy 5 (A), an extra chromosome X (B) and the Philadelphia chromosome (C)

frequent than the existence of sole or primary chromosomal abnormality [7]. The mechanism of trisomy 5, or any other chromosomal aneuploidy, in the pathogenesis of leukemogenesis remains unclear. Simple gene-dosage effect and the duplication of a mutation are considered to be two possible results of the gain of a whole chromosome [6]. It has been previously reported that dasatinib, multi-targeted tyrosine kinase inhibitor of BCR-ABL and SRC family kinases, plays an important role in the effective treatment of imatinib-resistant or intolerant Ph-positive ALL patients [10]. In our patient, dasatinib treatment resulted in complete remission. After treatment, bone marrow aspiration biopsy showed normal immunohistochemical staining, flow cytometry and cytogenetic results. Although the influence of additional aberrations on the result of the treatment with tyrosine kinase inhibitors in Ph-positive ALL requires large patient series, we think that our patient demonstrates a pioneer achievement during the course of ALL management.

Genes affected by chromosomal alterations tend to be involved in the pathways that control cell growth or development. Functional studies of these gene products may reveal the complex mechanisms playing a role in the pathogenesis of leukemogenesis and may help in the design of new therapeutic strategies.

Conflict of Interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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