A novel t(9;22;11) translocation involving 11q24 in a patient with chronic myeloid leukemia: A case report

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Abstract. Variant Philadelphia chromosome translocations involving chromosomes other than 9 and 22 have been reported in 5-10% of patients with chronic myeloid leukemia (CML). As part of the three-way variant t(9;22;11) in patients with CML, 11q24 is a novel region that has not previously been investigated. A 22-year-old male exhibiting chronic phase CML developed a recurrence of the same phase subsequent to the interruption of imatinib treatment and showed the same chromosomal abnormality, t(9;22;11)(q34;q11.2;q24), that was detected at the initial diagnosis. The recurrent CML responded well to imatinib therapy. These findings suggest that the three-way variant, t(9;22;11), involving 11q24 may be associated with a good prognosis and response to imatinib. This is the first report of three-way variant involving 11q24 in a patient with CML.

Introduction

Of patients with chronic myeloid leukemia (CML), 5-10% exhibit a Philadelphia (Ph) translocation variant involving ≥1 chromosomes in addition to chromosomes 9 and 22 (1). Although the distribution of the breakpoints exhibited a clearly nonrandom pattern in all chromosomes involved, there was a marked clustering in the chromosomal bands 1p36, 3p21, 5q13, 6p21, 9q22, 11q13, 12p13, 17p13, 17q21, 17q25, 19q13, 21q22, 22q12 and 22q13, suggesting that these regions may be particularly prone to breakage (2). The variant translocations affect additional chromosomal regions, producing different disease phenotypes. However, previous studies investigating ~100 cases of variant Ph chromosome translocations have not identified any impact on cytogenetic and molecular responses, or on patient outcome, compared with cases with a standard Ph chromosome (3,4). The majority of three-way t(9;22;11) variants of CML involve the 11q13 or 11p15 regions of chromosome 11 (1,5-11). The 11q24 region has not previously been investigated in a three-way Ph variant.

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Case presentation

A 22-year-old male was admitted to Chonbuk National University Hospital (Jeonju, Korea) for the evaluation and management of dizziness and severe leukocytosis in July 2011. The patient exhibited hepatosplenomegaly at admission without any other known chronic diseases. The initial complete blood count showed hemoglobin, 6.6 g/dl (normal range, 13-18 g/dl); platelets, 492.0x10^9/l (normal range, 150.0-450.0x10^9/l); and white blood cells, 590.8x10^9/l (normal range, 4.8-10.8x10^9/l) with 8.0% myeloblasts, 71.6% neutrophils, 4.5% lymphocytes, 4.5% monocytes, 9.1% eosinophils and 2.3% basophils. Bone marrow aspiration and biopsy findings were indicative of chronic phase CML with 8.0% of myeloblasts demonstrating granulocytic hyperplasia. The karyotype of the patient was 46, XY, t(9;22;11)(q34;q11.2;q24) in all metaphase cells analyzed (Fig. 1). A fluorescence *in situ* hybridization (FISH) analysis using a commercial BCR/ABL fusion probe (AbbottMolecular Inc., Des Plaines, IL, USA) identified the following out of total 200 interphase nuclei: 2 interphase nuclei with 1 single red signal (ABL1, 9q34), 1 single green signal (BCR, 22q11.2) and 2 fusion signals; 197 nuclei with 2 single red signals, 2 single green signals and 1 fusion signal; and 1 nucleus with 2 single reds, 1 single green and 1 fusion signal (Fig. 2A). MLL (11q23.1) break-apart FISH didn't show any rearrangement. Multiplex reverse transcription-polymerase chain reaction (RT-PCR) analysis using the Multiplex Nested RT-PCR HemaVision® kit (cat. no. HV01-28N; DNA Diagnostics, Risskov, Denmark) was performed according to manufacturer's instructions, with 2 sequential nested PCR reactions using primers included in the kit, in order to detect translocations. RNA was extracted from bone marrow samples using the High Pure RNA Isolation kit (Roche Diagnostics, Mannheim, Germany) as described previously (12). A major BCR-ABL fusion transcript, type b3a2, was detected. Thus, the patient was diagnosed with chronic phase CML,

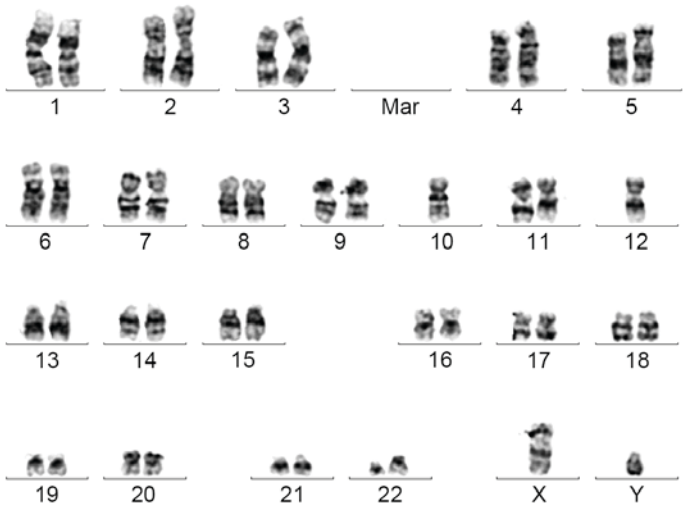

Figure 1. Representative image showing the three-way t(9;22;11) in a karyotype of the patient that was 46, XY,t(9;22;11)(q34;q11.2;q24). t, translocation.

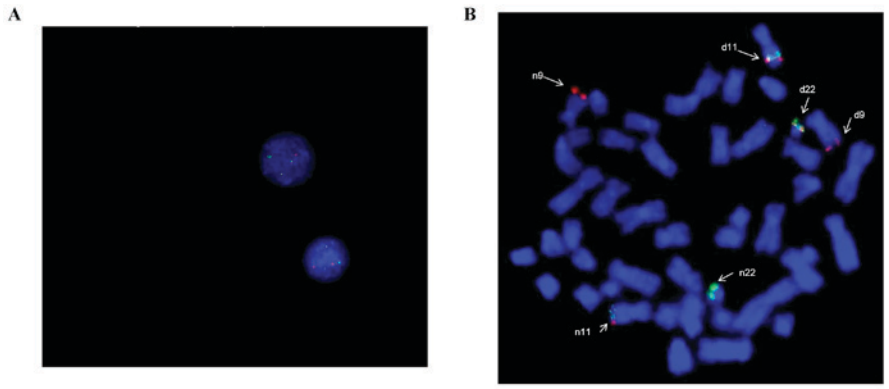

Figure 2. FISH images analyzed in (A) interphase (magnification, x400) and (B) metaphase cells (magnification, x1,000). In metaphase FISH analysis, BCR/Abelson murine leukemia viral oncogene homolog 1 dual fusion and MLL break-apart probes were used, revealing 2 fusion events. The first is a Philadelphia chromosome, indicated by arrow d22, and the second is derivative chromosome 11, on which BCR moved to 11q24. FISH, fluorescence *in situ* hybridization; n, normal; d, derivative.

and imatinib treatment was reinitiated. The patient had demonstrated a complete hematological response for 1 year subsequent to the start of treatment, but then stopped taking the medication. The patient was readmitted due to leukocytosis found in the laboratory test. Bone marrow findings showed that the initial diagnosis and the karyotype had not changed. Additional FISH analysis using BCR/ABL dual fusion and MLL break-apart probes revealed that the Ph chromosome was derived from a simple variant t(9;22) via a one-step mechanism, that ABL proto-oncogene 1 (c-ABL; 9q34, red) had moved to a BCR (22q11.2, green) and formed a fusion (Ph), BCR had moved to 11q24, and 11q24 moved to 9q34, whereas part of c-ABL remained, indicated by a red signal (Fig. 2B).

In contrast to the 2 expected fusion signals on classic Ph translocations, in the present study only 1 fusion signal was revealed, indicating a one-step mechanism, such as a simultaneous break in 9q34, 11q24 and 22q11.2 followed by a mismatched joining of the broken ends. Band 11q24 in this case has never been reported as a partner for Ph translocations.

Discussion

A three-way Ph translocation variant involving 11q24 associated with CML has never been described. Variant Ph translocations have been divided into simple variant translocations involving chromosome 22 and another chromosome, and complex variant translocations involving chromosomes 9 and 22 and 1-3 other chromosomes (2,13). Two different mechanisms are known to generate variant three-way translocations, a one-step mechanism in which chromosomal breaks occur simultaneously on 3 different chromosomes and a two-step mechanism involving 2 sequential translocations in which a standard t(9;22) translocation is followed by a second translocation involving additional chromosomes (14-16). The case presented in the present study was considered to be a simple variant translocation generated by a one-step mechanism. A variant translocation generated by a two-step mechanism is similar to clonal evolution, thus this mechanism may be associated with a poorer prognosis. The case of the present study showed a one-step variant translocation clinically identical to classic Ph translocations.

Variant translocations may possibly affect the course of the disease by altering the structure of the tyrosine kinase ligand binding site. Although numerous studies have addressed the possible effect of variant translocations on the clinical course of chronic phase CML, contradictory results have been reported (3,4,17). Previous studies have indicated that the clinical, prognostic and hematological features of types of CML exhibiting variant translocations are not distinct from types of CML exhibiting classic translocations, but the majority of these studies were based on a small series or literature reviews (2-4). Band 11q24, as a variant translocation partner, is a novel region that has not been investigated. Thus, the present study possessed no information on the clinical course or hematological features of CML with t(9;22;11)(q34;q11.2;q24). However, the patient of the present study experienced chronic phase CML twice with the same chromosomal abnormality, thus the clinical course between the first diagnosis and the relapse was compared. A three-way variant t(9;22;11) involving 11q24 was detected at the initial diagnosis, and the relapse samples indicated that the CML was in the chronic phase at the initial and relapse diagnoses. The clinical course of the patient was also similar prior and subsequent to relapse.

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