

Co-existence of isodicentric Ph chromosomes and the three-way Ph chromosome variant t(3;9;22)(p21;q34;q11) in a rare case of chronic myeloid leukemia

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Abstract. More than 90% of patients with chronic myeloid leukemia (CML) have the chromosomal translocation t(9;22)(q34;q11), while 5-8% of patients have complex variant translocations that have previously been thought not to affect the efficacy of imatinib therapy. The present study reports a patient with CML in B-lymphoid blast crisis who had a rare three-way Philadelphia (Ph) variant t(3;9;22)(p21;q34;q11), in addition to isodicentric Ph chromosomes. The patient was initially treated with imatinib for >2 months with a very poor response. When no T315I or F317L mutations in the ABL proto-oncogene 1 region were detected, the patient received dasatinib treatment (140 mg daily) and achieved a complete hematologic response. Following allo-hematopoietic stem cell transplantation, the patient displayed clinical, hematological and cytogenetic remission, with complete molecular response and complete donor chimerism, and stopped taking dasatinib at the last follow-up. The present data suggest that BCR-ABL gene amplification may be associated with imatinib resistance, which can be overcome with dasatinib. The present analysis suggests an alternative therapy strategy for CML involving isodicentric Ph chromosomes.

Introduction

Chronic myeloid leukemia (CML) is a clonal disorder characterized by the reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22)(q34;q11)]. This translocation,

which is present in 95% of patients with CML, creates a BCR, RhoGEF and GTPase activating protein (BCR)-ABL proto-oncogene 1 non-receptor tyrosine kinase (ABL) fusion gene that produces an abnormal tyrosine kinase. The imatinib mesylate is commonly used as the first-line oral treatment in patients with CML (1). It blocks the BCR-ABL tyrosine kinase activity and subsequently induces apoptosis, followed by a reduction in the proliferation of BCR-ABL-expressing cells (2). Therefore, the treatment of patients with CML with imatinib significantly increased survival and improved quality of life (3).

A small proportion of patients with CML (5-8%) present a more complex rearrangement of the Philadelphia (Ph) chromosome (4,5). These complex variant translocations and other mutations may be facilitated by genomic instability triggered by the t(9;22)(q34;q11) translocation, resulting in accelerated disease progression to blast crisis (6-8). How these events occur in detail remains unknown. The present report describes a patient with CML in B-lymphoid blast crisis who presented with a rare three-way Ph variant translocation t(3;9;22)(p21;q34;q11) in addition to isodicentric Ph chromosomes.

Materials and methods

Patient. A 42-year-old Chinese male was admitted to The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Zhejiang, China) in June 2011 because of neutrophilic granulocytosis and splenomegaly lasting the previous 6 months. Written informed consent from the patient was obtained for publication of this study. Hematological tests revealed a white blood cell count of $69 \times 10^9/l$ (normal range, $4-10 \times 10^9/l$), consisting of 67% neutrophils (normal range, 40-70%), 5% lymphocytes (normal range, 20-50%), 12% metamyelocytes (normal range, 0%), 10% myelocytes (normal range, 0%), 1% promyelocyte (normal range, $4-10 \times 10^9/l$), 1% eosinophils (normal range, 4-8%), 0.5% basophils (normal range, 0-1%) and 3.5% blasts (normal range, 0%); a platelet count of $499 \times 10^9/l$ (normal range, $100-300 \times 10^9/l$); and a hemoglobin concentration of 92 g/l (normal range, 120-160 g/l). Bone marrow examination revealed predominant granulopoiesis, a markedly elevated ratio of granulocytes to erythrocytes, and blasts cells

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accounting for 23% of all nucleated cells. Flow cytometry revealed high proportions of cells expressing CD10 (23%), CD19 (97%), CD13 (96.7%), CD33 (97.4%), HLA-DR (98.3%), and CD34 (85.8%). Reverse transcription-polymerase chain reaction (RT-PCR) revealed the presence of the p210-type (major) BCR-ABL fusion transcript (Fig. 1).

The patient was diagnosed with CML in B lymphoid blast crisis. He was initially treated with orally administered imatinib (600 mg daily), which was subsequently increased to 800 mg. This treatment was deemed ineffective after 65 days, when 13% of nucleated cells in bone marrow were found to be blast cells. Compared with the GeneBank sequence accession number NM_005157.5, no T315I or F317L mutations were observed in the ABL1 region. The patient was treated with dasatinib (140 mg daily) for 3 months, following which the patient displayed complete hematologic response. Later, the patient received hematopoietic stem cells from an HLA-matched sibling donor, and he underwent myeloablative conditioning. On day 126 following stem cell transplantation, immunosuppressive therapy was withdrawn and dasatinib therapy (140 mg daily) was again resumed.

At the last follow-up in September 2016, the patient was alive and displayed clinical, hematological and cytogenetic remission, with complete molecular response and complete donor chimerism (Table I). Dasatinib therapy was halted in May 2014.

Cytogenetic analysis. Unstimulated bone marrow was cultured for 24–48 h and chromosomes were prepared from these cultures using standard procedures. Chromosomes were analyzed in 20 metaphase cells using G-banding and R-banding, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature (9).

Fluorescence in situ hybridization (FISH). Chromosomes in 500 interphase nuclei cells were analyzed using commercially available FISH probes according to the manufacturers' instructions. The BCR-ABL fusion gene was detected using the probes ES-BCR-ABL and DF-BCR-ABL (GP Gene Company, Beijing, China), the region from the telomere of 22 to 22q11.1 downstream of the BCR breakpoint was detected using the breakpoint probe EWSR1 (22q12) (Anbiping Gene Company, Guangzhou, China), and the region from the centromere of chromosome 22 to 22q11.1 upstream of the BCR breakpoint was detected using the probe CSP22 (22q11) (GP Gene Company). The argininosuccinate synthase (ASS) probe (9q34.1; GP Gene Company) was used to detect the deletion range of ABL gene. The breakpoint probe BCL6 (3q27) (GP Gene Company) was used to detect the presence of 3q end.

RT-PCR. Total RNA was extracted immediately from fresh bone marrow cells of the patient. A negative control was used to monitor RNA isolation. Primers and RT-PCR analyses for transcripts of P210 type BCR/ABL, p190-type BCR/ABL and β -actin were performed as described previously (10).

Results

Chromosomal analysis at the time of diagnosis revealed 46, XY, idicder(22) t(3;9;22)(p21;q34;q11)[18]/46, XY, t(9;22)(q34;q11) (Figs. 2 and 3). These idic(Ph) chromosomes appeared identical

Table I. Evaluation of treatment in the chronic myeloid leukemia patient.

	Hematological response	Cytogenetic response	Molecular response
Imatinib	NR	NR	NR
Dasatinib	CHR	PCyR	<MMR
Allo-HSCT	CHR	CCyR	CMR

HSCT, hematopoietic stem cell transplantation; NR, no remission; CHR, complete hematological remission; PCyR, partial cytogenetic remission; MMR, major molecular response; CCyR, complete cytogenetic remission; CMR, complete molecular response.

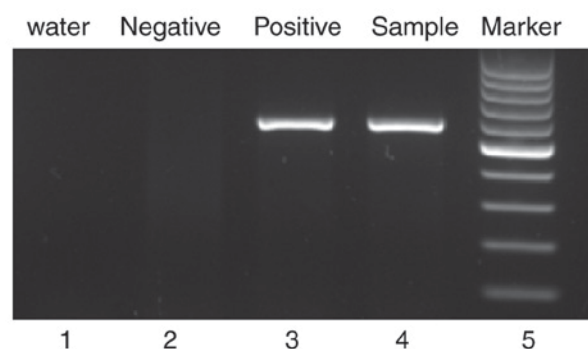


Figure 1. Reverse transcription-polymerase chain reaction reveals the presence of the p210-type (major) BCR-ABL fusion transcript. Lane 1, water; Lane 2, negative control; Lane 3, positive control; Lane 4, chronic myeloid leukemia diagnostic sample; Lane 5, marker.

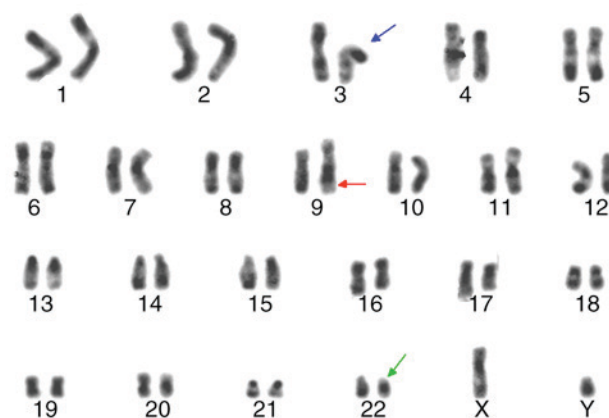


Figure 2. R-banding karyotype analysis demonstrates the isodicentric Ph chromosome (green arrow; end to end), der(9) (red arrow), and der(3) (blue arrow).

to normal chromosome 22 by R-banding, in contrast to idic(Ph) chromosomes fused at satellite regions on the p arms, which take on an equal length of two arms around centromeres (Fig. 2). G-banding analysis of the patient confirmed that the idic(Ph) chromosome was spindle-shaped, implying two Ph chromosomes joined at the q terminals (Fig. 3).

FISH analysis of nuclei of 200 interphase cells using the probes ES-BCR-ABL and DF-BCR-ABL revealed two non-overlapping fusion signals in 90% of cells (Fig. 4). These

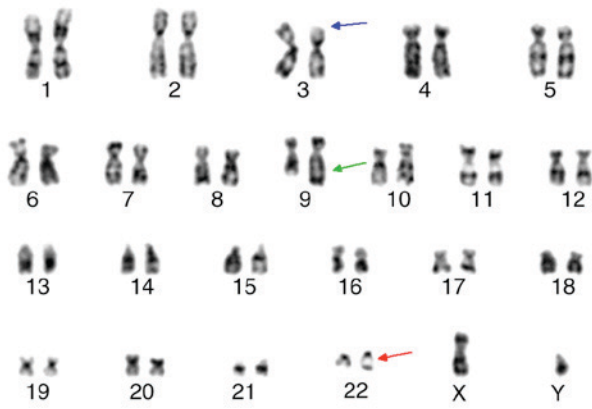


Figure 3. G-banding karyotype analysis demonstrates the spindle-shaped isodicentric Ph chromosome (red arrow; end to end), der(9) (green arrow), and der(3) (blue arrow).

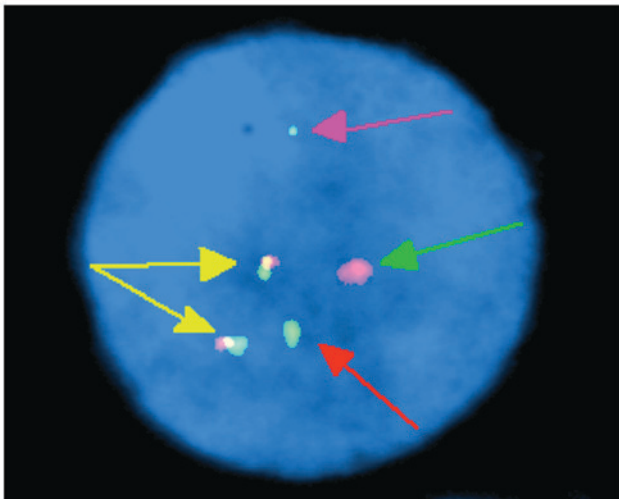


Figure 4. Photomicrograph of fluorescence *in situ* hybridization analysis of chromosomes from bone marrow cells using the probe DF-BCR-ABL. Formation of a Ph isochromosome is suggested by the presence of a single green signal corresponding to native BCR (red arrow), a large magenta signal corresponding to native ABL (green arrow), a smaller green signal corresponding to BCR on the der(3) chromosome (pink arrow), and two fusion signals corresponding to BCR-ABL fusions (yellow arrows).

results indicate that the idic(Ph) chromosome contained two BCR-ABL fusions. FISH analysis of metaphase chromosomes using the same two probes revealed the presence of two copies of the BCR-ABL fusion on one idic(Ph) chromosome and the deletion of ABL gene (Fig. 5), as well as the major breakpoint of BCR (Fig. 6). FISH analysis of interphase and metaphase chromosomes using the probe CSP16/22 revealed three copies of the BCR-ABL fusion on normal chromosome 22 and idic(Ph) (data not shown). FISH analysis using the EWSR1 (22q12) probe, which covers the downstream region of the BCR breakpoint, demonstrated two copies of the fusion on normal chromosome 22 and chromosome 3p- (data not shown). This result implied that the BCR-ABL fusion translocated to chromosome 3p-, and that the ABL and ASS genes were deleted. In addition, karyotyping analysis demonstrated that 3p21 exhibited deep R-banding originated from 22q11-ter, and 9q34 exhibited longer shallow R-banding than itself, which came from 3p21-pter (Fig. 3).

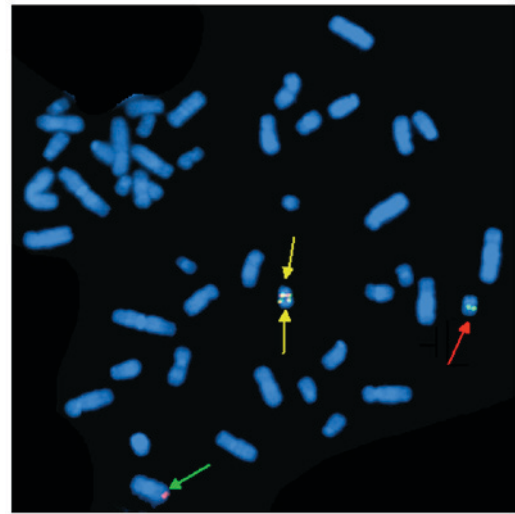


Figure 5. Photomicrograph of fluorescence *in situ* hybridization analysis of metaphase chromosomes from bone marrow cells using the probe ES-BCR-ABL. Formation of a Ph isochromosome is suggested by the presence of a large magenta signal on the normal chromosome 9, corresponding to native ABL (green arrow); one green signal on the normal 22 chromosome corresponding to native BCR (red arrow); and two fusions of signal on the chromosome 22 (yellow arrow).

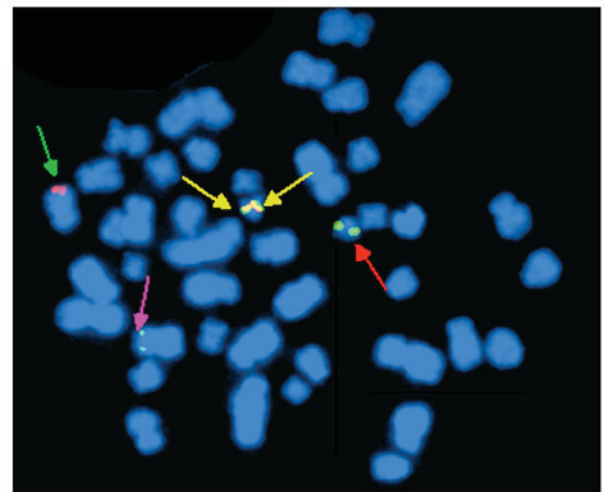


Figure 6. Photomicrograph of fluorescence *in situ* hybridization analysis of metaphase chromosomes from bone marrow cells using the probe DF-BCR-ABL. Formation of a Ph isochromosome is suggested by the presence of a large magenta signal on the normal chromosome 9, corresponding to native ABL (green arrow); a large green signal on the normal 22 chromosome, corresponding to native BCR (red arrow); one smaller green signal on the der(3), corresponding to BCR (pink arrow); and two fusions of magenta and green signal on the chromosome 22 (yellow arrow).

Furthermore, the BCL6 (3q27) gene was present on normal chromosome 3 and chromosome 3p-, confirming that 3p21 contained the breakpoint for formation of the variant Ph translocation in the CML patient (data not shown). The present results are consistent with three-way Ph translocation (P210 pattern).

Discussion

In rare cases, CML is associated with three-way Ph variant translocation involving chromosomes 9 and 22 (11,12). This

event occurs even more rarely in acute leukemia (13). Two main mechanisms have been proposed for three-way translocations: A one-step mechanism in which chromosome breakage occurs simultaneously on 3 chromosomes, which undergo 3-way translocation; and a two-step mechanism in which a standard t(9;22) translocation is followed by a second translocation involving additional chromosomes (4,14,15). The two-step mechanism may be associated with clonal evolution and poorer prognosis (14,15). The FISH pattern of the patient analyzed in the present study indicated one ABL copy (native), two BCR copies (one native and one on chromosome 3), and two copies of the BCR-ABL fusion on the idic(Ph) chromosome. This pattern is consistent with a two-step mechanism.

The present results provide evidence that the cytogenetic origins of CML may affect response to imatinib therapy and therefore patient prognosis. Prior to imatinib therapy becoming widespread, patients with variant translocations were considered to be at risk of poorer prognosis than those with the standard translocation (5,15-17). For example, the proportion of patients in the accelerated phase of CML was higher among those with variant translocations (56%) compared with those with classic translocations (38%) (16). Today, however, this prognostic distinction is considered controversial; for example, the European LeukemiaNet recommendations do not mention higher risk of poor prognosis for patients with CML with variant translocations (17). The present results suggest that the three-way translocation t(3;9;22)(p21;q34;q11) may be associated with poor prognosis of patients with CML treated with imatinib (18).

The implication of 3p21 in the present patient's three-way translocation may help explain the onset of CML. A total of 37 reports on CML patients with three-way Ph variant translocations involving chromosome 3 were identified in the Mitelman database (<https://cgap.nci.nih.gov/Chromosomes/Mitelman/>) and the recent literature (18,19), and the breakpoint in these patients occurs most often at 3p21. This region contains tumor suppressor genes (H37/Luca15/RBM5, RASSF1A) as well as tumor susceptibility genes (hMLH1) (20,21). Overexpression of H37/Luca15/RBM5 has been demonstrated to result in cell cycle arrest and apoptosis in human lung carcinoma (22). Deletions or translocations involving 3p21 have been linked to acute leukemia, myelodysplastic syndrome and solid tumor types, including small cell lung and renal cell carcinomas (21,23,24).

In addition to the three-way translocation t(3;9;22)(p21;q34;q11), the present patient possessed the idic(Ph) chromosome. First reported in 1973 (25), idic(Ph) is a rare cytogenetic aberration in which two identical Ph chromosomes fuse while retaining their centromeres. In the Mitelman database and the recent literature, there have been reports of 11 patients with CML and one patient with acute lymphoblastic leukemia that possess idic(Ph) chromosomes (26-31). In nearly all cases, these idic(Ph) chromosomes formed by fusion at the satellite region in 22p13 (27-29). In the present case, two previous cases of CML (30,31) and the single case with acute lymphoblastic leukemia (26), idic(Ph) chromosomes formed by fusion at 22q11. However, the causative factor of the formation of idic(Ph) chromosomes remains unknown. Isodicentric chromosomes may lead to breakage and reunion

cycles during mitosis, potentially forming ring chromosomes and thus leading to genomic instability and heterogeneity in the cell population.

The presence of the idic(Ph) chromosome in the present patient may also explain his poor response to imatinib. Often observed at later stages of CML, or in the accelerated phase of the disease, idic(Ph) chromosomes can be associated with resistance to standard chemotherapy and poor prognosis (28-30). In particular, higher copy numbers of idic(Ph) chromosomes result in amplification of the BCR-ABL gene, which is a key contributor to imatinib resistance (32,33). Indeed, the presence of a double Ph chromosome in patients with CML has been associated with poor response to imatinib but good response to dasatinib (34,35). This is consistent the present study, where the patient responded well to dasatinib.

In conclusion, the present study described for the first time the presence of a three-way Ph variant t(3;9;22)(p21;q34;q11) and isodicentric Ph chromosomes in a CML patient. These results may help define a new therapeutic standard for treating CML involving isodicentric Ph chromosomes.

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