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Three-way complex variant translocation involving short arm chromosome (1;9;22)(p36;q34;q11) in a chronic myeloid leukemia patient

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Abstract. Chronic myeloid leukemia (CML) is a disease of the clonal hematopoietic stem cells caused by a balanced translocation between the long arms of chromosomes 9 and 22. Overall, 90-95% of CML patients present with a Philadelphia (Ph) chromosome t(9;22)(q34;q11) translocation and in addition, variant complex translocations, involving a third chromosome, are observed in 5-8% of CML patients. Cytogenic testing using bone marrow sample was performed and the FISH test was used for the detection of BCR-ABL fusion gene and complete blood analysis of CML patient was also performed. Results of hematological analysis showed the induced values of white blood cells (168,5000/mm^3) and platelets (300,000/mm^3) and FISH analysis test showed that 98% cells were positive for BCR/ABL gene translocation. The present study describes a three-way (1;9;22)(p36;q34;q11) Ph chromosome translocation in a 24-year-old female with CML. The patient, who was in the chronic phase of the disease, was treated with daily dose of 400 mg/dl with imatinib mesylateand was monitored constantly at various intervals over a 6-month period. Many studies reported that certain CML patents with variant translocation responded poorly to imatinib. In the current case report, the CML patient exhibited a suboptimal response to imatinib, denoting a poor prognosis.

Introduction

Chronic myeloid leukemia (CML) is a disease of the clonal hematopoietic stem cells caused by a balanced translocation between the long arms of chromosomes 9 and 22. The t(9;22)(q13;q11) translocation is known as the Philadelphia (Ph) chromosome or translocation (1); it results in an increase in the number of myeloid cells, erythroid cells and platelets in the peripheral blood, and causes myeloid hyperplasia in the bone marrow (2). The Ph-positive translocation between chromosomes 9 and 22 (q34;q11) is found in ~95% of CML patients (3,4). In addition, more complex rearrangements of the Ph chromosome are observed in 5-8% of CML patients. In these cases, additional Ph chromosome translocations are involved (5-7). Imatinib mesylate is a protein tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase produced by the Ph chromosome in patients with CML. Imatinib mesylate blocks the proliferation and induces the apoptosis of Bcr-Abl-expressing cells in patients with CML and acute lymphoblastic leukemia. The treatment of CML with imatinib has proven successful, with increased survival rates and improved quality of life (8-10). The present study describes the case of a 24-year-old female with chronic-phase CML who presented with a three-way (1;9;22)(p36;q34;q11) Ph chromosome translocation. The rearrangement was analyzed by cytogenetic and fluorescence *in situ* hybridization (FISH) tests.

Case report

Patient presentation. A 24-year-old female was diagnosed with CML on April 6, 2011. The hematological analysis revealed a white blood cell (WBC) count of 168,500/mm^3 (normal range, 4000-11000/mm^3), a red blood cell (RBC) count of 3.1 m/mm^3,(normal range, 4-6m/mm^3), a hemoglobin (Hb) level of 6.7 g/dl (normal range, 12-16 g/dl), a packed cell volume of 22.7 g/dl (normal range, 16.5-18.0 g/dl), a mean corpuscular volume (MCV) of 71.2 fl (normal range, 76-96 fl), a mean corpuscular hemoglobin (MCH) level of 21.0 pg (normal range, 28-32 pg), an MCH concentration (MCHC) of 29.5 g/dl (normal range, 32-36 g/dl), a platelet count of 300,000/mm^3 (normal range, 150,000-400,000/mm^3), a mature neutrophil value of 55% (normal range, 40-70%), an immature lymphocyte value of 6% (20-45%), a myelocyte value of 7% (normal value, 0%), a metamyelocyte value of 13% (normal value, 0%), a stab cell value of 19% (normal range, 0-3%), a normoblast

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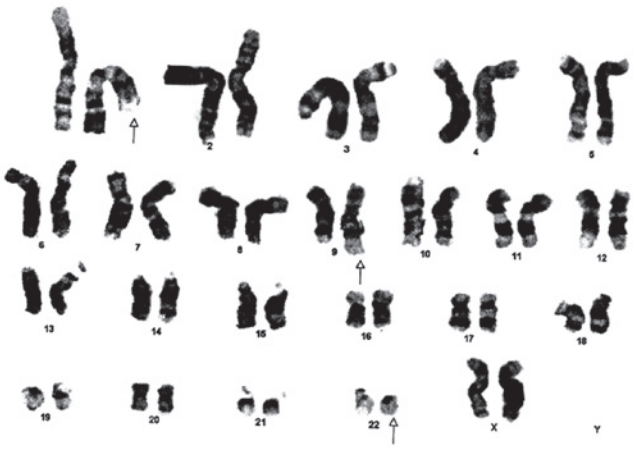

Figure 1. Cytogenetic analysis revealing a variant three-way (1;9;22)(p36;q34;q11) 46XX translocation. The derivative chromosomes are highlighted by arrow heads.

count of 07/100 WBCs (normal value, 0/100 WBCs) and an erythrocyte sedimentation rate of 50 mm/h (normal range, 0-29 mm/h). The indicative significant symptoms were depression, anxiety, sleep disturbance, fever, weight loss, swelling of the face, hands and feet, and blurred vision. An abdominal ultrasound report revealed enlargement of the liver, which measured 17.3 cm cranio-caudally in the mid lavicular line (normal value, 15 cm). The portal vein diameter was increased, measuring 18.1 mm. The spleen was also enlarged, measuring 35.5 cm (normal value, 13 cm). Hepatitis B surface antigen and anti-hepatitis C tests were performed using an immunochromatographic screening method, but the results were negative.

Complete blood cell analysis. The hematological analyzer that was used for the complete blood count measured the level of WBCs, RBCs, platelets and Hb, the MCV, MCH, MCHC and hematocrit level, and the red cell distribution width. Hematological analysis revealed a WBC count of 168,500/mm^3, a platelet count of 300,000/mm^3 and a Hb level of 6.5, which indicated anemia in the patient. Patients with CML usually demonstrate high levels of WBCs and platelets. These investigations usually enable a diagnosis of leukemia to be established or discounted. The present patient was advised to undergo further tests.

Cytogenetic analysis. Cytogenetic analysis was performed on the bone marrow culture using a standard technique (11). In total, 20 GTG banded bone marrow metaphase cells were analyzed. The karyotypes were named according to the International System for Human Cytogenetic Nomenclature (12). The cytogenetic analysis of the 20 metaphase cells from the patient identified the presence of a complex, three-way (1;9;22)(p36;q34;q11) Ph chromosome translocation (Fig. 1). A segment of chromosome 9, distal to 9q34, had been translocated onto chromosome 22 at band 22q11.2, a segment of chromosome 22, distal to q11.2, had been translocated onto chromosome 1 at 1p36.1, and a segment of chromosome 1, proximal to 1p36.1, had been translocated onto chromosome 22 at 22q11.2.

FISH. FISH orange and green dual color fusion probes were used to detect the presence of Bcr-Abl translocations in 500 interphase nuclei cells. FISH revealed that 98% of the cells analyzed were positive for the Bcr-Abl gene translocation.

Treatment. The patient was treated with antibiotics and Gleevec (imatinib). Initially, the patient was treated with orally administered imatinib at a daily dose of 400 mg, and subsequently this initial daily dose was increased from to 600 mg. To date, the patient has been receiving treatment for 39 months. The patient was of middle-class socioeconomic status and was fully aware of her condition.

Discussion

A positive (9;22)(q34;q11) Ph translocation is present in ~90% of CML patients with chronic-phase disease. However, only 5-8% of patients demonstrate complex Ph chromosome variants, in which a third chromosome, in addition to chromosome 9 or 22, is involved (5,7). This chromosome, referred to as the Philadelphia chromosome, is responsible for the production of a protein BCR-ABL fusion gene which possesses protein kinase activity. The BCR-ABL gene interferes with white blood cells, which consequently disrupts the body's immune response. To the best of our knowledge, only a small number of previous cases have been reported with such complex rearrangements (13). Aguayo *et al* (14) reported that individuals of 55-60 years of age, were more likely to be affected by CML, however, all age groups including infants may also be affected (10% of cases) (1,13). Faderel *et al* (3) reported 15% adults and 12-30% older age patients (>60 years) were also affected by CML. In this study the age range was found to be between 25-35 years (3). Mkrtchyan *et al* (15) proposed two possible mechanisms which may be involved in the formation of variant or complex translocations. The first is a single event rearrangement by way of the simultaneous breakage of several chromosomes followed by mismatched joining. The second is a multi-step mechanism in which a classical Ph translocation is followed by further translocation events involving chromosomes 9 and 22, plus a third, fourth, fifth and potentially sixth translocation event, referred to as four, five or six-way translocation.

The present study described a three-way translocation, 46XX t(1;9;22)(p36;q34;q11). Additionally, 98% of the cells analyzed by FISH were positive for the Bcr-Abl gene translocation. Variations in the FISH signal pattern were also observed. Furthermore, the sequence within the breakpoint region on chromosomes 1, 9 and 22 was detected due to its complex or variant translocation.

The patient was treated with 400-600 mg/day Gleevec. Imatinib is a protein tyrosine kinase inhibitor that inhibits the constitutively active, abnormal Bcr-Abl tyrosine kinase produced by the Ph chromosome in patients with CML. In addition, imatinib inhibits the receptor tyrosine kinases associated with platelet-derived growth factor, stem cell factor and c-Kit. The treatment of CML with imatinib has proven successful, with increased survival rates and improved quality life (16,17).

In conclusion, the present study reported a rare case of chronic phase CML with a positive Bcr-Abl transcript involving a three-way (1;9;22)(p36;q34;q11) Ph chromosome translocation.

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