Complex chromosomal rearrangements involving five chromosomes in chronic myelogenous leukemia: A case report

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Received February 16, 2015; Accepted January 18, 2016

DOI: 10.3892/ol.2016.4275

Abstract. The typical breakpoint cluster region/Abelson (BCR-ABL) fusion gene, which is located in the Philadelphia chromosome, in association with a complex translocation event is only observed in 2-10% of patients with chronic myelogenous leukemia (CML). CML is diagnosed based on the presence of splenomegaly, increased peripheral white blood cells and the expression of BCR-ABL. The present study reports the case of a patient with CML that possessed complex aberrations involving 5 chromosome translocations, which consisted of t(1;6)(p36.1;q25) and t(9;22;11)(q34;q11.2;q11). After 2 months of follow-up, the patient is in remission following treatment with imatinib (400 mg/day) and hydroxyurea (3,000 mg/day). The hematological parameters of the patient were significantly improved and the white blood cell count returned to normal (from $361.00x10^9$ cells/l to $6.83x10^9$ cells/l; normal range, $3.50\text{-}9.50x10^9$ cells/l). The results of the ultrasonic examination revealed that the presence of splenomegaly had disappeared, indicating that the treatment strategy was effective. According to the outcome of the treatment, hydroxyurea in combination with imatinib is recommended for use in similar cases of CML.

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that originates from abnormal pluripotent bone marrow stem cells and is consistently associated with the breakpoint cluster region/Abelson (BCR/ABL) fusion gene, which is located in the Philadelphia (Ph) chromosome (1-4). CML is diagnosed based on the presence of splenomegaly, increased peripheral white blood cells and the expression of BCR-ABL. Usually, 90-95% of CML cases in the chronic phase of disease have the characteristic t(9;22)(q34;q11.2) reciprocal translocation that results in the Ph chromosome (2,5). In such cases, the BCR/ABL fusion gene is present and may be identified using fluorescence *in situ* hybridization (FISH) analysis, reverse transcription-polymerase chain reaction (RT-PCR) or Southern blot analysis techniques (6). In Ph^+ CML patients, increased tyrosine kinase activity and the presence of the BCR/ABL chimeric protein p210 are required for multiple pathways to confer the leukemia phenotype (7). CML cases with complex chromosomal aberrations that involve additional chromosomes have been reported (8).

Imatinib, also termed Gleevec or Glivec, is a tyrosine kinase inhibitor that inhibits the tyrosine kinase activity of the BCR/ABL protein. Imatinib is widely used as an initial treatment for newly-diagnosed CML patients in the chronic phase of disease. In >95% patients, a complete hematological response may be induced by imatinib and a complete cytogenetic response may be induced in >75% of patients. Patients that are treated with imatinib reported an improved quality of life (9). However, resistance to imatinib remains to be a challenging obstacle to achieving a better clinical outcome. Therefore, optimized combinations of drugs are required to be developed to improve the treatment of CML.

The present study reports the case of a CML patient with novel complex aberrations that involved 5 chromosome translocations, the symptoms of which were improved by treatment with imatinib and hydroxyurea.

Case report

A 37-year-old male patient was admitted to Jining No. 1 People's Hospital (Jining, China) on June 24, 2013, with progressive weight loss and a cough that had lasted for two months. The ultrasonic examination (MyLab™ClassC; Esaote China Ltd., Hong Kong, China) revealed splenomegaly, a white blood cell (WBC) count of $361.0x10^9$ cells/l (normal range, $3.5\text{-}9.5x10^9$ cells/l), 0.64% eosinophils (normal range, 0.4-8.0%) and a platelet count of $226x10^9$ platelets/l (normal range, $150\text{-}400x10^9$ platelets/l). The serum parameters of the patient were as follows: Serum lactic dehydrogenase, 1092.0 units/l (normal range, 218.0-458.0 units/l); γ-glutamyltranspeptadase, 61.8 units/l (normal range, 3.0-50.0 units/l); hydroxybutyrate dehydrogenase, 876.0 units/l (normal range, 61.0-155.0 units/l); triglyceride, 2.49 mmol/l (normal range, 0.45-1.81 mmol/l);

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Key words: breakpoint cluster region/Abelson, Philadelphia chromosome, chronic myelogenous leukemia

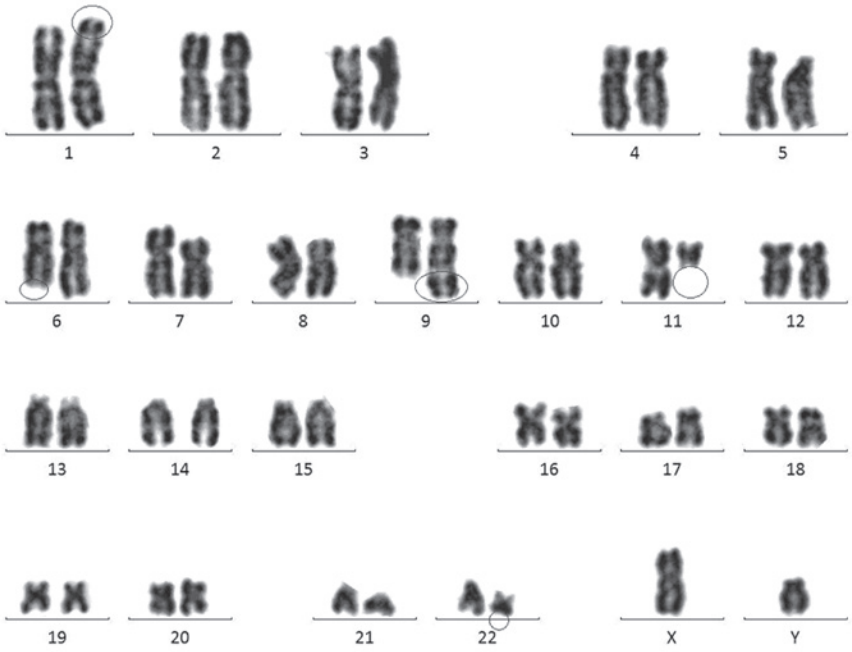

Figure 1. Giemsa-banding revealed a complex karyotype involving three other chromosomes in addition to Philadelphia chromosomes. All derivative chromosomes are marked by a circle.

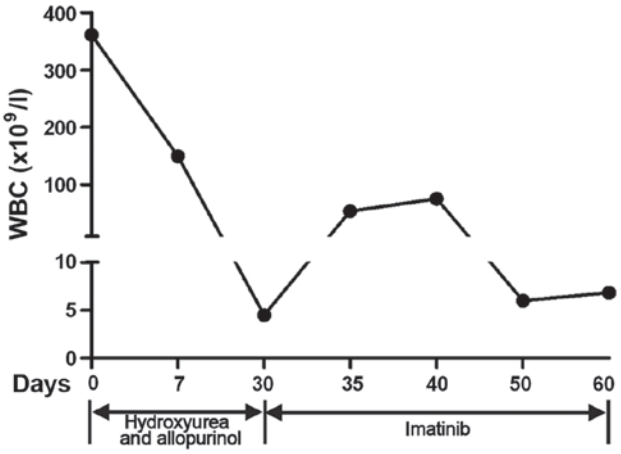

Figure 2. Change in the WBC count of the patient during treatment. The patient was initially treated with hydroxyurea and allopurinol for 30 days and then imatinib was used. The WBC count was determined at various time points. WBC, white blood cell.

β2-microglobulin probe 3, 82 mg/l (normal range, 0.8-2.4 mg/l); and blood sugar, 2.23 mmol/l (normal range, 3.9-6.1 mmol/l), as measured using an chemistry analyzer (AU680, Beckman Coulter, Inc., Brea, CA, USA).

The Giemsa (GTG)-banding technique was performed for chromosome analysis, according to the manufacturer's protocol (10). A total of 20 metaphases that were obtained from the unstimulated bone marrow of the patient were analyzed, and the karyotypes were described according to the International System for Human Cytogenetic Nomenclature (11). Karyotyping was performed prior to the initiation of chemotherapy treatment and the t(1;6)(p36.1;q25) and t(9;22;11)(q34;q11.2;q11) karyotype changes were observed (Fig. 1). Amplification of the BCR-ABL gene was performed and the results were as follows: BCR-ABL/ABL, 48.97%; ABL gene copy, $2.63x10^5$; and major-BCR (p210) copy, $1.29x10^5$.

The patient was treated with hydroxyurea (3,000 mg/day) and allopurinol (3,000 mg/day). Subsequent to 1 week of treatment, the WBC count of the patient had decreased to $149.9x10^9$ cells/l, and the other hematological parameters were 1.34% monocytes and 1.84% eosinophils. The concentration of hemoglobin was 86 g/dl (normal range, 120-160 g/dl) and the platelet count was $172x10^9$ platelets/l. One month later, the WBC count dropped to $4.49x10^9$ cells/l, the hemoglobin B concentration was 91 g/dl and the platelet count was $258x10^9$ platelets/l. In addition, the splenomegaly became less evident. Following these improvements, 400 mg/day imatinib was administered for an additional 10 days. Notably, the WBC count had increased to $54x10^9$ cells/l with 6.84% lymphocytes, 8.64% monocytes and 1.14% eosinophils 5 days subsequent to treatment with imatinib. The hemoglobin and platelet counts were 103 g/dl and $260x10^9$ platelets/l, respectively. Following 10 days of treatment, the WBC count was $75.29x10^9$ cells/l. Subsequent to the continued use of imatinib for an additional 30 days, the WBC count and spleen returned to normal (Fig. 2). As the spleen had returned to normal, the patient continued treatment at home with imitinib for 6 months. A follow-up appointment 6 months later confirmed that the patient remained disease-free. Informed consent was obtained from the present patient for the publication of the present case report.

Discussion

The cytogenetic hallmark of CML, such as the Ph chromosome and complex chromosomal rearrangements that involve additional chromosomes, have also been described in numerous studies (8,10-12). In the present study, the case of a

rare Ph chromosome-positive patient with CML and a novel complex variant translocation t(1;6), t(9;22;11) was reported. Following treatment with imatinib and hydroxyurea, the WBC count and the condition of the spleen returned to normal, which indicated that the combined treatment was an effective strategy.

In total, ~5% of CML patients demonstrate the involvement of one or more chromosomal translocations, in addition to the Ph chromosome (5). In the present study, the involvement of chromosomes 1, 6, 9, 11 and 22 was detected. The typical Ph chromosome demonstrating BCBCR/ABL fusion was detected using GTG-binding and PCR. In addition, t(1;6)(p36.1;q25) and t(9;22;11)(q34;q11.2;q11) were also detected using GTG-binding analysis. Notably, a rare translocation of 11q11 between chromosomes 9 and 22 was indicated in the present study. To the best of our knowledge, the translocation with t(1;6)(p36.1;q25) and t(9;22;11)(q34;q11.2;q11) has never been described in the literature. The formation of variant translocations that involve various chromosomes may have prognostic importance (13).

Following the diagnosis, the present patient was initially treated with hydroxyurea and allopurinol and then treated with imatinib continually to maintain the improvement. The hematological parameters of the patient were significantly improved and the WBC count returned to normal. The signs of splenomegaly disappeared, indicating that the combination treatment strategy was effective.

In conclusion, the present study reported the rare case of a Ph chromosome-positive patient with CML in the chronic phase of disease and novel complex aberrations that involved the t(1;6)(p36.1;q25) and t(9;22;11)(q34;q11.2;q11) translocations. According to the outcome of treatment, hydroxyurea in combination with imatinib is recommended for use in similar CML cases.

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