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CASE REPORT

A unique case of complex variant translocation of t(6;9;22)(p22;q34;q11.2), der(19) in a newly diagnosed patient with chronic myeloid leukemia

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Abstract

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the dysregulated production and uncontrolled proliferation of myeloid neoplastic cells. CML is associated with the fusion of BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene. The translocation of chromosomes (9;22)(q34;p15) is present in almost 90–95% of patients with CML and only 5–8% CML patients have established variant complex translocation due to the participation of one or more chromosomes other than 9 and 22 chromosome. In the present study, a unique case of a pH chromosome-positive CML is reported with a new variant pH translocation involving three chromosomal aberrations 6p22, 9q34, 22q11.2 and derivation 19 which has not been described previously. The complex variant translocation with pH chromosome was 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2] in this newly diagnosed CML patient. Additional cytogenetic anomalies may be seen in patients which are not controlled by the tyrosine kinase inhibitor in CML patients or in accelerated/blastic phase. In this case, the patient' treatment was switched to dasatinib because the IS-NCN could not be controlled with imatinib. In conclusion, complex translocations in unusual locations of the BCR / ABL gene appear to indicate a poor prognosis.

Keywords Chronic myeloid leukemia, Philadelphia chromosome, Translocation of chromosomes.

Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplastic disease characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with relatively normal differentiation. CML is associated with the fusion of two genes, BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene [1]. The abnormal gene fusion results from a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11) that gives cause to an abnormal chromosome 22 called the Philadelphia (pH) chromosome [2]. The translocation of chromosomes (9;22)(q34;p15) is regarded in almost 90–95% of patients with CML and only 5–8% CML patients have established variant complex translocations, which are due to the participation of one or more chromosomes other than 9 and 22 chromosome [3,4]. In those cases, at least, a third chromosome other than 9 and 22 is involved. The segment from the third chromosome is usually translocated to the 9q34 band, however the 22q11→22qter region moves to the breakpoint of the third chromosome [5]. In some cases of CML, fluorescence in situ hybridization (FISH) disclosed the translocation of 3′ ABL sequences from 9q34 to 22q11 adjacent to the 5′ portion of the BCR gene with the

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formation of the BCR/ABL hybrid gene [6]. In the newly diagnosed chronic phase CML patients, only t(9;22) is detected. Additional cytogenetic anomalies are seen in patients who cannot be controlled by tyrosine kinase inhibitor or in accelerated/blastic phase CML patients [7] In the present study, a unique three-way pH-positive complex variant translocation 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2] is reported in a newly diagnosed CML patient.

Patient and methods

Case report

A 43 year-old-male patient admitted to Hematology clinic because of fatigue, weight loss, sweating and pain in the left upper quadrant in May 2018. The laboratory study of the patient were, WBC (163,000/mm3), hemoglobin (10.9 g/dl), platelets (139,000/mm3), MCV (91 FL), HCT (33%), lymphocytes (6%) and neutrophils (25%). Peripheral blood contained immature myeloid cells (promyelocytes 8%, myelocytes 20%, metamyelocytes 35%, normoblasts 5%), some blasts (2%) and basophils (2%). LDH was 716 U/l (normal, $<$248 U/l) and serum alkaline phosphase was 113 U/l (normal, 30–120 U/l). The ultrasound imaging report of patient showed mild hepatomegaly and massive splenomegaly. Bone marrow biopsy showed myeloid hyperplasia with a dominence of immature cells and increased megakaryocytes. Cytogenetic analysis yielded abnormal metaphases: 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2]. Patient was diagnosed as CML by bone marrow biopsy and cytogenetic analyses. Reverse transcription–polymerase chain reaction (RT-PCR) showed the presence of p210-type BCR–ABL fusion transcript. IS-NCN (International Scale for RT-PCR monitoring for CML patients) was calculated as 11.0 from peripheral blood sample at diagnosis. IS-NCN was calculated as 61.4 from bone marrow biopsy material at diagnosis. Oral treatment was initiated immediately with imatinib mesylate 400 mg/day. Imatinib mesylate was administered for four months and after this period re-calculated IS-NCN was higher than the previous value of 61.4. Because of the higher IS-NCN value, treatment modality was changed and dasatinib treatment has been initiated in November 2018.

Methods

Bone marrow culture was used for cytogenetic analysis. Chromosome analysis using GTG-banding was performed according to standard procedures [8]. A total of 20 metaphase cells derived from the bone marrow of the patient were analyzed. Karyotype analyses were characterized according to the international system for cytogenetic nomenclature [9]. Serial Bcr-Abl RT-PCR monitoring considered as standard clinical practice after CML diagnose. RT-PCR monitoring assay required to be optimized in different labs. It is more sensitive to use IS scale (BCR-ABL/ABL ratio%) in CML patients for RT-PCR monitoring [10].

Results

The cytogenetic karyotyping results of the patient showed 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2] (Fig. 1). Histopathological examination of bone marrow revealed hypercellularity with increased myeloid/erythroid ratio and increased basophils in smears of aspiration material (Fig. 2). Furthermore, RT-PCR showed the presence of the p210-type BCR-ABL fusion transcript. The patient's laboratory studies showed a decrease in WBC 8900/mm^3 and an increase in hemoglobin (11.9 mg/dl) in the follow up. However, his IS-NCN value increased from 11.0 to 61.4. Like some reported cases with unusual locations of the BCR/ABL gene seem to indicate this patient has a poor prognosis. After the treatment with dasatinib, the hemoglobin value of the patient increased to 12.7 mg/dl and white blood cell count was 9600/mm^3. Also under treatment of dasatinib, patient's last IS-NCN decreased to 1.1.

Discussion

Variant Philadelphia translocations involving chromosome 6 are a very rare events and the translocation in the presented case involving 6p22 have not been reported previously. The distribution of the break-points is non-random with the chromosomal bands most susceptible to break being: 1p36, 3p21, 5q31, 6p21, 9q22, 10q22, 11q13, 12p13, 17p13, 17q21, 17q25, 19q13, 21q22, 22q12 and 22q13 [11]. The genetic mechanisms and clinical significance of the variant pH translocations are still uncertain. Morel et al. predicted a two-step mechanism. The first one includes the formation of (9;22)(34q;11q) translocation. The second is the further translocation involving a derivative chromosome from pH translocation and a third chromosome [12]. The available results provide evidence that the variant translocation in CML patients may affect response to imatinib therapy and therefore patient prognosis [13,14]. The percentage of patients in accelerated phase of CML was higher in CML patients with variant translocations compared to CML patients with classic translocations (56% vs 38%) [15]. Various side effects were seen in patients under imatinib treatment [16]. Therefore, patients with a complex karyotype should be closely monitored for both side effects and disease progression under tyrosine kinase inhibitor treatment. Jacobo et al. evaluated 51 patients with CML in blastic phase in order to identify prognostic factors for complete hematologic response and survival. The study showed that, age $>$ 60 years, hemoglobin $<$ 10 g/dL, and complex karyotype were statistically significant negative prognostic factors for OS in multivariate analysis. Allogeneic hematopoietic stem cell transplantation may be considered in choice of treatment of those patients in early period due to poor prognosis because the disease cannot be controlled by tyrosine kinase inhibitors.

In the present study, a unique case of a pH chromosome-positive CML with a new variant pH translocation involving three chromosomal aberrations 6p22, 9q34, 22q11.2 and derivation 19 was reported, which has not been described previously. The complex variant translocation with pH chromosome was 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2]. The clinical course of the patient was in a manner with poor prognosis. Additional cytogenetic anomalies may be seen in patients who are not controlled by tyrosine kinase inhibitors in CML patients or in the patients with accelerated/blastic phase. In this case, the patient's treatment was switched to dasatinib because the IS-NCN could not be

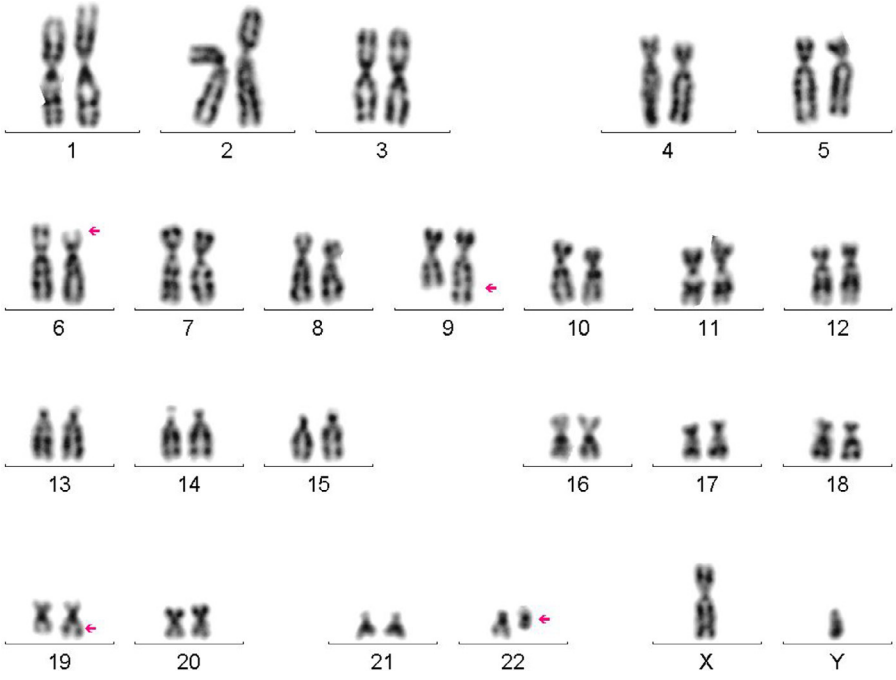

Fig. 1 Cytogenetic analysis shows a variant three-way translocation 46,XY,t(6;9;22)(p22:q34;q11.2), der(19)[48]/46,XY[2]. Arrowheads highlight all derivative chromosomes.

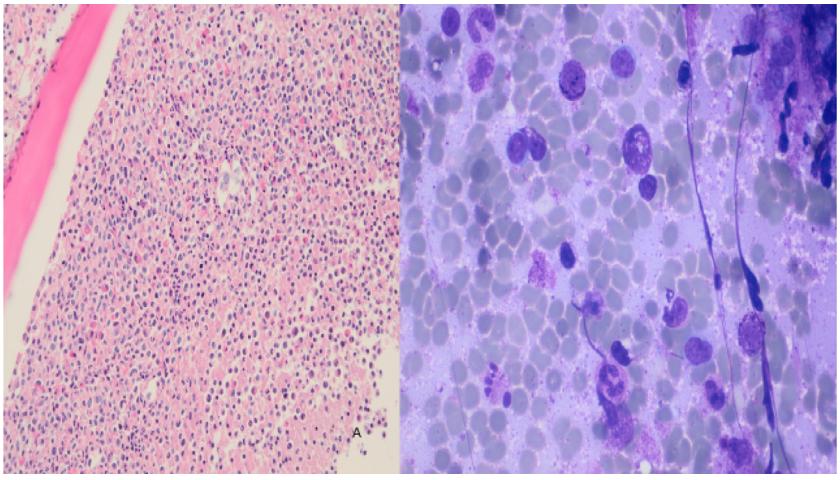

Fig. 2 A: Hypercellular bone marrow biopsy with increased myeloid/erythroid ratio, B: Increased basophils in the bone marrow aspiration smear.

controlled with imatinib. In conclusion, complex translocations in unusual locations of the BCR / ABL gene appear to indicate a poor prognosis.

Conflict of interests

The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Role of the funding source

None.

Informed consent statement

Informed consent was obtained from patient included in the study.

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