

A Chronic Myeloid Leukemia with a Unique Variant Philadelphia Chromosome Translocation: t(9;22;19)(q34;q11.2;p13)

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Chronic myeloid leukemia (CML) is categorized as one of the myeloproliferative neoplasms, according to the World Health Organization (WHO) myeloid neoplasms and acute leukemia classification. The hallmark of this disease is the presence of a reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22)(q34;q11)] which leads to the formation of the Philadelphia chromosome (Ph) and is present in 90%-95% of CML patients. In 5%-10% of CML cases, there are variants where one or more different chromosomes are involved in addition to chromosome 9 and 22.

We present a patient with newly diagnosed CML with a rare variant translocation involving chromosomes 9, 19 and 22. To the best of our knowledge, this is the first case study to describe a variant Ph chromosome translocation in chronic phase CML in Bahrain.

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Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder from the group of myeloproliferative neoplasms, according to the WHO myeloid neoplasms and acute leukemia classification; it accounts for 15% of newly diagnosed cases of leukemia in adults^{1,2}. CML represents 11.7% of the total hematological malignancies in Bahrain³.

The cytogenetic hallmark of the disease is a reciprocal translocation t(9;22)(q34;q11.2) between the ABL (Abelson murine leukemia) gene on chromosome 9 and the BCR (breakpoint cluster region) gene on chromosome 22, with subsequent formation of Ph chromosome which encodes an oncoprotein with constitutively active tyrosine kinase activity that activates downstream pathways and promotes the growth and replication of the myeloid cell line⁴.

While Ph chromosome is detected in 90%-95 % of patients with CML, variant Ph chromosome translocations have been reported in 5%-10% of patients with newly diagnosed CML. These variants are characterized by the involvement of one or more chromosomes in addition to chromosomes 9 and 22, and should be distinguished from additional chromosomal abnormalities emerging during treatment or clonal evolution that drives disease progression and obscures the prognosis¹.

Fluorescence in situ hybridization (FISH) using a locus-specific dual-color, dual-fusion probe is essential in identifying and confirming translocations. With the dual-color, dual-fusion BCR/ABL1 probe, the normal signal pattern consists of two red and two green signals (2R 2G) on the normal chromosomes 9 and 22, respectively. When the t(9;22) is present, the typical BCR/ABL1 fusion pattern (2F 1R 1G) consists of two fusions (2F), one red (1R) and one green (1G) signal; however, at least five atypical fusion patterns can be found⁵.

The mechanism of variant Ph generation and the molecular basis of biological differences between classic Ph and variant Ph chromosomes are not fully understood, but it has been revealed that variant Ph does not impact the response to medication or clinical outcome⁶.

The aim of this presentation is to report a newly diagnosed case of CML in the chronic phase (CP) with an atypical variant translocation involving chromosomes 9, 19, and 22.

THE CASE

A thirty-one-year-old female patient with no history of any significant medical illness was admitted in September 2016

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with generalized headache and body weakness for two weeks, associated with blurred vision, nausea but no vomiting and loss of 3 kg in about 22 days.

Investigation revealed hemoglobin of 7.6 g/dL, platelets $369 \times 10^9/L$, WBC count $135 \times 10^9/L$ and a differential consisting of lymphocytes 4%, segmented neutrophils 24%, bands 28%, metamyelocytes 3%, myelocytes 20%, promyelocytes 6%, blasts 3%, eosinophils 4%, monocytes 5% and basophils 3%.

Bone marrow aspiration was hypercellular, with hyperplastic granulopoietic system, myeloid to erythroid ratio was 10:1 with increased basophils and eosinophils and one percent of blasts. Bone marrow biopsy showed hypercellular marrow with >95% cellularity, reversed myeloid to erythroid ratio, marked myeloid hyperplasia, prominent left-shift with focal collections of immature myeloid cells and increased eosinophils.

Chromosome analysis using GTG-banding was performed according to standard procedures. A total of 25 metaphase cells derived from the unstimulated bone marrow were analyzed. Karyotype was described according to the International System of Human Cytogenetic Nomenclature (ISCN) 2016⁷.

The result showed a female karyotype 46, XX, t (9;22;19)(q34;q11.2;p13), with a variant translocation involving chromosome 9, 22 at breakpoint region q34, q11,2 (BCR/ABL1) and the third chromosome 19 at p13 region respectively, see figure 1.

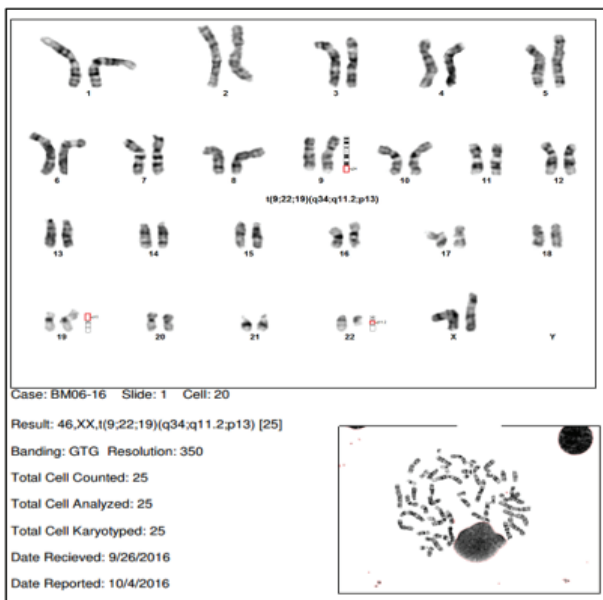


Figure 1: GTG-Banding Chromosomal Karyotype Showing a Female Karyotype with Chronic Myeloid Leukemia with a Three-Way Translocation, T(9;22;19) (Q34;Q11.2;P13)

FISH using a BCR-ABL dual-color, dual-fusion translocation probe (probe combination: ABL1-9q34 region – spectrum red; BCR -22q11.2 region – spectrum green) was performed. A total of 200 interphase cells were analyzed. The result showed fusion positivity for BCR/ABL1. In all the positive cells, an atypical signal pattern of two red, two green (1F, 2R, 2G) was observed, indicating the variant translocation, see figure 2.

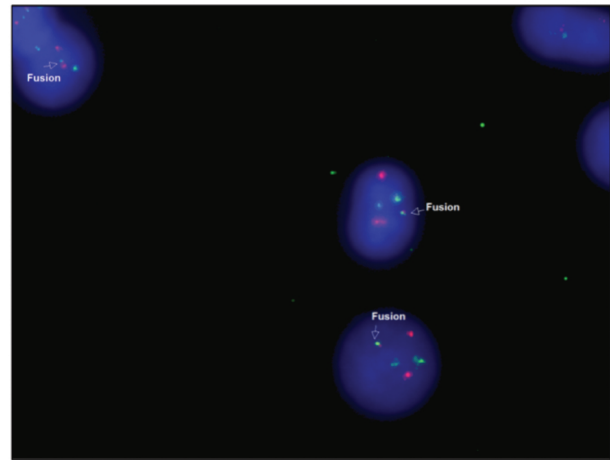


Figure 2: Fluorescent in Situ Hybridization (FISH) Analysis of Ph Positive Cells Metaphase Showing 1 Fusion, 2 Green, 2 Red, Confirming the Atypical Pattern of Variant Chronic Myeloid Leukemia

The patient received prophylaxis for tumor lysis syndrome (intravenous fluids and allopurinol) and hydroxyurea until the diagnosis of CP- CML was confirmed, after which, she was started on imatinib (Gleevec) 400 mg daily.

DISCUSSION

Two types of variant translocations were documented, simple variant translocation and complex variant translocation. The simple variant translocation occurs when only one other chromosome is involved in addition to chromosomes 9 and 22, and the complex variant translocation occurs when two or more chromosomes take part in the translocation. All chromosomes can be involved in translocations except for chromosome Y⁸.

Our patient is a case of simple translocation, where chromosome 19 is involved in addition to chromosomes 9 and 22, leading to a three-way translocation, t (9;22;19)(q34; q11.2; p13). The translocation has been described previously, but few cases have been recognized. In one study of 559 patients, the variant translocation occurred in 30 patients (5%), but chromosome 19 was involved in only one case⁹. Another study found 50 (5.1%) variant translocations among 1,071 newly diagnosed patients with CML, chromosome 19 were involved in the translocation in only one case, showing the rarity of this involvement¹⁰.

In our patient, the breakpoint region of chromosome 19 was at 19p13. Involvement of an identical region was described in the first study mentioned above, but not in the second one^{9,10}.

The molecular genesis for variant translocations has not been completely understood, but most probably occurred in a “one step” or “two-step” process. In the first mechanism, three chromosomes break and rejoin simultaneously, in the “two-step” mechanism, a standard two-way translocation (9;22) occurs followed by subsequent rearrangements involving other chromosomes^{11,12}.

The typical FISH pattern seen with the one-step mechanism is 1F2G2R, while the pattern for the two-step mechanism can be variable (2F1G1R, 1F1G1R, 1F1G2R, 1F2G1R, etc.)^{13,14}.

The FISH pattern in our case was 1F2G2R, corresponding to the “one step” process, which is more frequent type in the literature^{9,13}.

Concerns regarding the prognostic significance of these variant translocations have been risen, especially regarding imatinib response; however, several studies have shown that these translocations do not impact the prognosis or even the outcome in the tyrosine kinase inhibitors era, especially in simple variant translocations^{6,9,15,16}.

CONCLUSION

We report a newly diagnosed case of CML in the CP with a simple variant translocation involving three chromosomes, 9q34,22q11.2, and 19p13 identified by the FISH method. The clinical significance of these Ph chromosomes variants remains unclear and apparently has no impact on the response to tyrosine kinase inhibitors.

The recognition of these cases will shed light on the leukemogenesis process and can be the basis for the development of new treatment strategies in the cases with no optimal response.

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