A novel three-way Philadelphia Variant t(9;22;17)(q34;q11.2;q12) in chronic myeloid leukemia: A case report

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Abstract. Chronic myeloid leukemia (CML) is a hematologic malignancy associated with increased circulating myeloid cells and platelets in the peripheral blood, with accompanying bone marrow hyperplasia. The Philadelphia chromosome, t(9;22)(q34;q11), is present in 95% of CML patients, resulting in constitutive tyrosine kinase activity; however, ~5% of CML patients possess a Philadelphia variant. A novel three-way Philadelphia translocation variant, t(9;22;17)(q34;q11.2;q11.2), was identified in a 54-year old man who presented with leukocytosis, anemia and thrombocytosis that was diagnosed with chronic myeloid leukemia, chronic phase. Cytogenetic analysis by G-banding revealed the presence of a three-way translocation involving the long arms of chromosomes 9, 22 and 17. Fluorescence in situ hybridization utilizing a dual-color fusion probe confirmed the presence of the Bcr-Abl fusion gene.

Case report

In January of 2017, a 54 year old man was transferred to our institution from an outside facility with leukocytosis, anemia, and thrombocytosis. His hematologic parameters were as follows: White blood cells 84.2 K/ul, red blood cells 3.96 M/ul, hemoglobin 10.5 g/dl, hematocrit 32.1%, red cell distribution width 19.0%, and platelets 641 K/ul. A peripheral blood film showed increased polychromasia and increased anisocytosis and poikilocytosis, with acanthocytes, schistocytes, dacryocytes, and elliptocytes identified. There was a left shift in the peripheral granulocyte population, with a manual differential count finding 1% blasts, 1% promyelocytes, 11% myelocytes, 8% metamyelocytes, 10% neutrophils, 45% segmented neutrophils, 3% eosinophils, 4% basophils, 8% lymphocytes, and 9% monocytes.

The bone marrow aspirate showed hypercellular particles and a left shift in the myelocyte peak, with 5% erythroid precursors, 2% myeloid blasts, 7% promyelocytes, 42% myelocytes, 23% metamyelocytes and bands, 18% neutrophils, and 3% eosinophils.

On flow cytometry analysis of the bone marrow, 84% of cells fell within the granulocyte gate, 8% in the nucleated red blood cell gate, and 2% each in the lymphocyte gate, CD45 dim gate, and monocyte gate. The gated population of CD45 dim cells showed partial expression of early markers CD117 and CD34, consistent with myeloid blasts (0.4% of total cell population).

Cytogenetic analysis was performed on bone marrow cells collected at the time of primary diagnosis and cultured using standard techniques. From this, twenty GTG banded metaphase cells were analyzed and all were found to possess a complex, three-way (9;22;17)(q34;q11.2;q11.2) Philadelphia chromosome translocation (Fig. 1). Further analysis by fluorescence in situ hybridization (FISH) utilizing dual-color fusion probes confirmed the presence of Bcr-Abl translocation in 86 out of 100 interphase cells (Fig. 2).

Discussion

The Philadelphia chromosome t(9;22)(q34;q11) is present in greater than 90% of CML patients, however approximately 5% of patients demonstrate variants in which a third chromosome in addition to chromosomes 9 and 22 is also involved (1). These complex three-way translocations could be formed by two mechanisms. Either there could be a one-step translocation...
involving three chromosomes at the same time, or a two-step mechanism where first a typical t(9;22) translocation occurs, followed by a second translocation between the aberrant chromosome 9 or 22 and the 3rd chromosome (2). The most frequently involved chromosomes in variant Philadelphia translocation are 3p21, 3q21, 11q13, 12p13, and 17q25 (3). Other chromosomes that have been rarely involved in variant Philadelphia translocation include 4q25 (4), 10p11.2 (5), 11p15 (6), 17p11.2 (7), and 21p12 (8). One uniting factor, however, is that all of these variants ultimately lead to a Bcr-Abl fusion gene (3,9). The exact translocation present in our patient has not been previously reported, however analysis by FISH confirmed the presence of a Bcr-Able fusion gene.

The clinical presentation of CML patients with variant Philadelphia chromosomes is indistinguishable from that of patients with the classic translocation. Additionally, several reports have found that Philadelphia chromosome variant patients tend to have a similar prognosis to those with the classic Philadelphia translocation when treated with imatinib therapy (10).

In conclusion, we report a rare case of chronic phase CML with a novel complex three-way Philadelphia variant t(9;22;17) (q34;q11.2;q12).

References


Figure 2. Dual-color fluorescence in situ hybridization probe showing one green (Bcr) signal on chromosome 22, one large orange (Abl) signal on chromosome 9, one yellow fusion signal (Bcr-Abl), and a small orange signal showing the residual Abl on chromosome 9. This confirms the presence of Philadelphia chromosome translocation.

Figure 1. G-banded karyotype showing 46, XY, t(9;22;17)(q34.1q11.2;q11.2).