A Chronic Myelogenous Leukemia (CML) Case with a Cryptic Insertion of the ABL1 Gene of Chromosome 9 into 22 Resulting in a Fusion Signal on the Derivative 22: 46,XY.ish ins(22;9)(q11.2;q34q34)BCR+,ABL1+

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Abstract

Chronic myelogenous leukemia (CML) is characterized by the specific cytogenetic translocation t(9;22)(q34;q11.2), also called the Philadelphia (Ph) chromosome. We present a case of a cryptic BCR/ABL1 fusion, which was not originally detected by standard karyotyping. The patient is a forty-seven-year-old man who presented with leukocytosis. Conventional cytogenetic studies revealed a 46,XY karyotype. Despite this finding, the patient was started on hydroxyurea therapy followed by Gleevec. At six-month follow-up, a repeat karyotype was again normal, though FISH analysis was positive for BCR/ABL1 fusion. FISH performed on previously G-banded metaphases showed a very rare cryptic insertion involving 22q11. While most genetic abnormalities in CML can be diagnosed using classical cytogenetics, molecular studies remain the gold standard in definitively identifying the characteristic BCR/ABL1 fusion. This case represents one of the variant cryptic rearrangements in CML where clinical correlation with morphologic, immunophenotypic, cytogenetics and FISH findings are indicated and highlights the importance of molecular testing at the time of primary diagnosis.

Case Study

Chronic myelogenous leukemia (CML) is a hematological neoplasm that classically presents with hypercellular bone marrow, with myeloid preponderance, splenomegaly, granulocytosis, and thrombocytosis (Monma et al., 2004). The cytogenetic hallmark in CML is the Philadelphia chromosome (Ph) – present in up to 95 percent of cases (Monma et al., 2004). This results in a BCR/ABL1 fusion gene with constitutive tyrosine kinase activity, which seems to be the critical factor in the leukemogenesis process. The remaining 5 percent of cases (Monma et al., 2004) show genetic variants of the Philadelphia chromosome involving a third chromosome. Around 1 percent of CML cases appear to have a Philadelphia negative karyotype but carry a cryptic BCR/ABL1 fusion that can be identified by fluorescence in situ hybridization (FISH) (Monma et al., 2004).

Herein, we report a case with a very rare cryptic translocation which required FISH studies to detect the diagnostic cytogenetic abnormality that was missed by conventional chromosome studies. A 49-year-old male presented with splenomegaly, vertigo, and high WBC count (>700,000/mL). Bone marrow (BM) biopsy showed hypercellular marrow with marked myeloid preponderance. Flow cytometry detected a small population of myeloblasts (0.84%) with aberrant CD7 expression; granulocytes and monocytes showed partial CD56 expression. Karyotype revealed no cytogenetic abnormality. PCR testing was performed on peripheral blood and was positive for the BCR/ABL1 fusion transcript with a ratio of 11.173, confirming the diagnosis of CML. Hydroxyurea and Gleevec therapy was given, and after six months, the WBC count had decreased to 53,000/mL. Repeat bone marrow biopsy showed persistent CML in chronic phase. Gleevec dose was increased, but soon reduced secondary to pancytopenia, which persisted, and the patient was switched to Sprycel. The most recent follow-up showed normalization of WBC counts (42,000/mL) with only mild anemia (Hb 9.6 g/dL) and pancytopenia (67 x 109/L).

Cytogenetic studies of the BM showed 46,XY[20] (Figure 1). FISH analysis was performed on interphase nuclei as well as in previously G-banded metaphases using the Vysis LSI BCR/ABL Dual color, Dual Fusion Translocation probe from Abbott Molecular (Des Plaines, Illinois 60018) on interphase nuclei and in previously G-banded metaphases. A fusion signal appeared in 195 (97.5%) of the 200 interphase nuclei analyzed (Figure 2A). Seventeen of the 195 cells (8.7% of the abnormal cells) also showed an extra green signal for the BCR gene (data not shown). FISH analysis on abnormal previously G-banded metaphases confirmed a cryptic translocation of the ABL1 gene from chromosome 9 into chromosome 22, yielding a yellow fusion signal on chromosome 22 (Figure 2B). The results support a diagnosis

Figure 1. Karyotype of our patient: 46,XY.ish ins(22;9)(q11.2;q34q34)BCR+,ABL1+
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The gold standard in CML diagnosis involves detection of BCR/ABL fusion, which may require molecular testing. Our case illustrates the importance of a multidisciplinary approach including clinical, morphologic, immunophenotypic, cytogenetic, and molecular correlation.

References


Wan TSK, Ma SK, Li CK, Chan LC. Atypical fluorescence in situ hybridisation pattern in chronic myeloid leukaemia due to cryptic insertion of BCR at 9q34. Leukemia. 2004; 18:161-162.

Author Details

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