Case Report

Coexistence of p190 BCR/ABL Transcript and CALR 52-bp Deletion in Chronic Myeloid Leukemia Blast Crisis: A Case Report

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Abstract. We introduce a 78-year-old woman presented with thrombocytosis and high blast count who had a history of splenectomy. Her cytogenetic analysis revealed aberrant chromosomal rearrangements in different clonal populations harboring 46XX karyotype with t(9;22) (q34;q11). RT-PCR assay detected the e1a2 BCR-ABL translocation resulting from rearrangement of the minor breakpoint cluster region (m-bcr) in BCR gene. Subsequent evaluation of the disease showed calreticulin (CALR) 52-bp deletion as well as the absence of JAK2V617F heterozygous mutation in granulocyte population of peripheral blood using allele-specific PCR and bi-directional DNA sequencing. To our knowledge, this is the first case of a patient initially diagnosed as p190 BCR-ABL transcript positive CML in blast crisis characterized by a 52-bp deletion in CALR gene.


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Introduction. Chronic myeloid leukemia (CML) is the most important myeloproliferative neoplasm (MPN) developed due to the known t(9;22)(q34;q11) chromosomal translocation in pluripotential hematopoietic progenitor cells. This genetic alteration results in the formation of Philadelphia chromosome (Ph), comprising portions of Abelson (abl) and breakpoint cluster region (bcr) genes.¹² This fusion transcript is present in 90-95% of patients with CML and serves as diagnostic and prognostic biomarker. It is also a therapeutic target in cases with a wide spectrum of clinical symptoms, including hypercellular bone marrow (BM), splenomegaly, anemia or platelet dysfunction as well as significant increase in the number of leukocytes, especially neutrophils and immature myeloid cells.³ Unlike the common form of p210 BCR-ABL oncprotein, in which the breakpoint occurs between exon 2 of abl gene on chromosome 9 and exons e12–e16 of the bcr gene on chromosome 22, the first exon of bcr gene is involved in this translocation in 1-2% of CML patients. This rare fusion transcript, also known as minor breakpoint cluster region (m-bcr), codes for a smaller (190kDa) oncprotein with a unique clinical presentation between CML and chronic myelomonocytic leukemia (CMML).⁴ Besides the identification of mutations in Janus kinase 2 (JAK2) and thrombopoietin receptor (MPL) genes BCR/ABL negative MPNs, calreticulin (CALR) gene mutations have also been used in classification and determination of diagnostic criteria for MPNs and myelodysplastic/myeloproliferative neoplasms.
(MDS/MPN), including essential thrombocythemia (ET), primary myelofibrosis (PMF) and refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T), respectively.\(^5\) Insertion/deletion mutations in exon 9 of CALR does not occur in CML, but some authors have recently reported the existence of these somatic changes in remaining portions of nonmutated JAK2 and MPL MPN cases.\(^6\)

We report the case of a CML patient with p190 type BCR-ABL transcript who also harbored CALR 52-bp deletion. Beyond a few studies of CML patients with p190 kDa fusion protein,\(^7\) to the best of our knowledge, this is the first report to describe the coexistence of P190 BCR/ABL transcript and CALR 52-bp deletion in blast crisis in a CML patient. Herewith, we have presented a detailed insight into the study of clinical and molecular cytogenetic findings to assess the prognostic information in guiding management strategies for our patient.

**Case report.** A 78-year-old woman was admitted to our department in May 2015 with pallor, weakness and a remote history of splenectomy. Her peripheral blood (PB) revealed anemia with a hemoglobin concentration of 8.6 g/dL, thrombocytosis (789,000×10\(^3\)/µL), white blood cell (WBC) count of 68200/µL with 16% neutrophils, 1% eosinophils, 1% monocytes, 48% lymphocytes, 16% atypical lymphocytes and 18% blasts. Morphologic review of the PB smear revealed basket cells and nucleated red blood cells. BM aspirate smears showed hypercellular marrow with increased blasts (Figure 1A) and platelets (Figure 1B). Blasts

![Figure 1. A, B: Increased blasts and platelets in BM examination of initial diagnosis. C, D: Chromosomal aberrations revealed in cytogenetic analysis. E: FISH indicated the rearrangement between ABL and BCR genes. F: Bi-directional sequencing for confirmation of CALR 52-bp mutation.](image-url)
showed a fine chromatin pattern, round nuclei, and scanty cytoplasm.

Cytogenetic analysis indicated the presence of der(11), der(17) and der(18) chromosome abnormalities in different clonal populations harboring 46XX karyotype with t(9;22) (q34;q11) (Figure 1C, 1D) in addition to the observed BCR-ABL fusion gene in BM metaphases by fluorescence in situ hybridization (FISH) (Figure 1E). In the first step of verification at the molecular level, RT-PCR was performed for detection of p210-type mRNA as previously described, but sequence analysis of amplification products did not show the p210 BCR-ABL positive rearrangement. This result prompted us to investigate p190BCR-ABL mRNA fusion transcript by RT-PCR assay according to standard procedures, which was positive in our patient similar to rare cases of CML with an inferior outcome of therapy.

The initial manifestation of the disease was an overwhelming splenomegaly; however, the patient was referred to our center with a high platelet count anterior to splenectomy. In consideration of the possibility of a chronic myeloproliferative disease transformed in the acute phase, it has been carried out allele sequencing in the following investigations (including a high platelet count and the abnormally to detect the mutation JAK2V617F during treatment. It has been carried out allele rearrangement identifi
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References:

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In summary, this interesting case illustrates that CALR 52-bp deletion may act as a distinctive feature in the diagnosis of p190 BCR-ABL/CML patients. Questions remain regarding the exact contribution of CALR deletion to MPNs.


