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LETTER TO THE EDITOR

Rare Case of Co-Occurrence of BCR::ABL1 and CBFB::MYH11 in Chronic Myeloid Leukemia Blast Crisis

Fang Long [1], Man Chen [2], Ting Li [3], Minjing Fu [3], Aixian Wang [2], Hui Wang [2]

Fang Long and Man Chen contributed equally to this work
[1] Department of Clinical Laboratory, Sichuan Provincial Women's and Children's Hospital/The Affiliated Women's and Children's Hospital of Chengdu Medical College, Chengdu, Sichuan Province, 610000, China
[2] Department of Laboratory Medicine, Hebei Yanda Lu Daopei Hospital, Langfang, 065201, China
[3] Department of Laboratory Medicine, Beijing Lu Daopei Hospital, Beijing, 100176, China

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Correspondence:
Hui Wang
Department of Laboratory Medicine
Hebei Yanda Ludaopei Hospital
Sipulan Road
Yanjiao Development Area
Langfang, 065201
China
Email: ldpwanghui2022@163.com

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CML is a clonal myeloproliferative neoplasm, characterized by the presence of BCR/ABL fusion gene, which results from the reciprocal translocation between chromosomes 9 and 22 (Philadelphia Ph) [1]. This translocation is also detected in a small number of B-cell lymphoblastic leukemia (B-ALL) and less frequently in de novo AML [2]. The most common form of BCR-ABL1 fusion in CML results in a 210 kDa product, whereas in B-ALL the main fusion form results in the 190 kDa product. The inv(16)(p13.1q22) or less commonly t(16;16)(p13.1;q22), which fuses the CBFB gene to the MYH11 gene, belongs to one of the AML with recurrent genetic abnormalities. It was designated as M4Eo in the French-America-British (FAB) cooperative group classification and is considered as a favorable prognosis [3]. However, the co-occurrence of inv(16) and t(9;22) carrying P190 BCR/ABL1 is very unusual in a 35-year-old male of CML-BC. Its prognostic significance in these diseases remains largely unknown.

A 35-year-old male patient with a 3-month history of chronic-phase chronic myeloid leukemia (CML-CP) presented with cough and sputum for one week. Three months ago, the boy was admitted to hospital for ophthalmic examination due to “blurred vision in both eyes”. A complete blood count showed an extremely

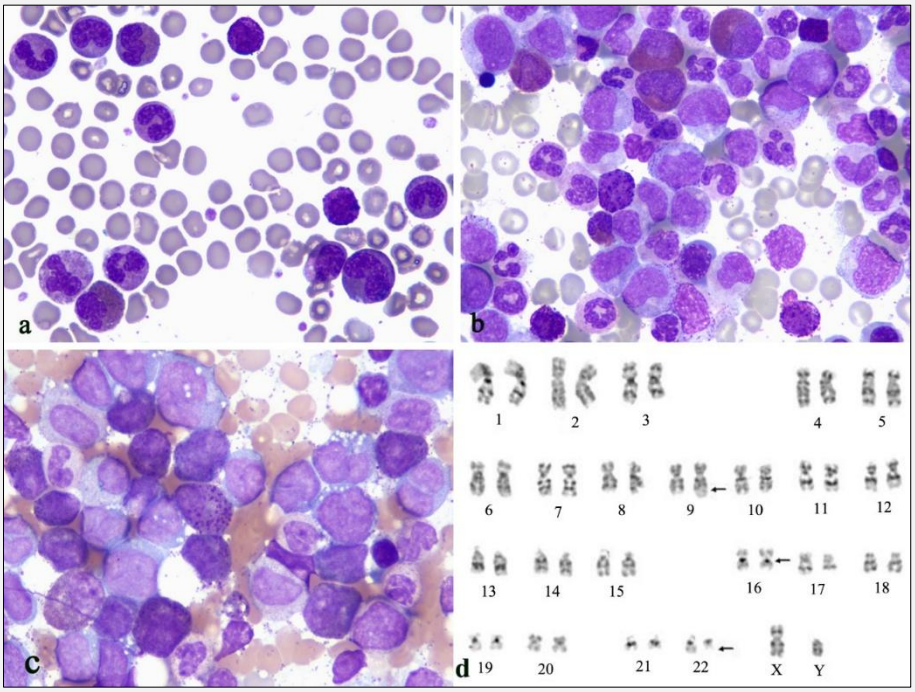

Figure 1. a - b in CML-CP: The peripheral blood smear shows a significant increase of eosinophils and basophils (a, Wright-Giemsa, x 1,000), the bone marrow (BM) aspirate smear revealed hypercellular, with 2% blasts, 7% eosinophils and 3.5% basophils (b, Wright-Giemsa, x 1,000), c - d in CML-BP with inv(16): The BM aspirate showed 18.5% blasts, 15.5% eosinophils, 1% basophils, and atypical large purple granules were observed in the eosinophils (c, Wright-Giemsa stain, x 1,000) Cytogenetic analysis revealed coexistence of t(9;22)(q24;q11.2) and inv(16)(p13.1q22) in all 20 cells analyzed (d).

high level of white blood cells of 294 x 10^9/L, hemoglobin concentration of 94 g/L and platelets of 551 x 10^9/L. Physical examination showed no hepatosplenomegaly. Peripheral blood (PB) smear showed a significant increase of eosinophils and basophils (Figure 1a), the bone marrow (BM) aspirate smear revealed extremely hypercellular, with 2% blasts, 7% eosinophils and 3.5% basophils (Figure 1b). Cytogenetic analysis showed 46,XY,t(9;22)(q34;q11.2) [20]. BCR-ABL1 (p-190 fusion protein) was detected by real-time quantitative (RT-PCR). Therefore, the initial diagnosis of CML-CP was made. He was admitted to hospital and had presented with cough and sputum for one week. The CT scan of the whole abdomen showed slight hepatosplenomegaly. Complete blood count results revealed remarkable leukocytosis (66.4 x 10^9/L), hemoglobin concentration of 139 g/L and platelet count of 123 x 10^9/L. The blood smear showed 85% blasts, the BM aspirate revealed 18.5% blasts, 15.5% eosinophils, and 1% basophils. Simultaneously, atypical large purple granules were observed in several eosinophils (Figure 1c), suggesting the possibility of CML-BP. Flow cytometry identified 42.5% abnormal cells expressed CD33, CD33, CD117, cMPO, HLA-DR, CD34 (partial) and CD38 (partial). Cytogenetic analysis revealed coexistence of t(9;22)(q24;q11.2) and inv(16)(p13.1q22) in all 20 cells analyzed (Figure 1d). BCR-ABL1^{P190} and CBFB-MYH11 were positive by RT-PCR.

Cases of CML were classified as chronic phase (CP), accelerated phase (AP), or blast crisis (BC) according to criteria of the World Health Organization classification of neoplastic diseases of hematopoietic and lymphoid tissue [1]. Cytogenetics and molecular biology play an important role in the subclassification and risk stratification of myeloid neoplasms. The inversion 16(p13q22) or t(16;16) has been recognized as a feature of myelomonocytic differentiation, abnormal eosinophils, with a good prognosis [3]. It was also designated as M4Eo in the French-America-British (FAB) cooperative group classification. The presence of BCR-ABL1 created by t(9;22)(q34;q11.2), is the hallmark of CML. Almost all patients with typical CML, including CML-BC, show a major breakpoint cluster region located between exons 12 and 16, with a 210 kDa chimera protein size of BCR/ABL (P210), whereas a small subset of patients with B-ALL, along with less commonly de novo AML usually

possess a p190 BCR-ABL1 [2]. Progression of CML is usually associated with clonal evolution; when transforming to AP or BC, up to 80% of the cases demonstrate cytogenetic changes in addition to the Ph chromosome, such as a second Ph chromosome, trisomy 8, trisomy 19, and isochromosome 17q [1].

As far as we know, the coexistence of BCR-ABL1 and CBFB-MYH11 is an extremely rare event with less than a total of 40 cases reported in the literature, with a marked adult predominance [4-10]. We herein describe an infrequent patient with CBFB rearrangement and P190 BCR/ABL1 in CML-BC. Moreover, it's worth noting that all this clinical information combined with the history of CML with abnormal eosinophils and blasts observed on the BM smears, suggesting a possibility of CML-BP by acquiring CBFB rearrangement. Upon reviewing the existing literature, we observed that the majority of patients with a prior history of chronic-phase chronic myeloid leukemia (CML-CP) typically harbor the p210 kD BCR-ABL1 fusion protein. In contrast, our case involves the less common p190 BCR-ABL1 variant. In general, patients exhibiting both BCR-ABL1 and CBFB rearrangements can be categorized into two principal groups: those with a clinical course beginning as CML-CP that subsequently progresses to blast phase (CML-BP) through acquisition of inv(16)(p13q22), and those with de novo acute myeloid leukemia (AML) in whom both genetic alterations are identified at diagnosis. While flow cytometry is not routinely employed in the monitoring of CML, some studies have proposed that minimal residual disease (MRD) panels designed for AML may offer clinical utility in tracking disease progression in patients harboring both inv(16) and BCR-ABL1 rearrangements [5].

To the best of our knowledge, patients with CML-BP often have an adverse prognosis. Some scholars have indicated that patients with BCR-ABL1 positive AML with inv(16) have a relatively favorable prognosis, similar to AML with inv(16) alone [10]. However, in our case, the patient never received CR, following the eventual diagnosis of CML-BP. Lately, one study found that patients with coexisting inv(16) and BCR-ABL1 may benefit from intensive chemotherapy regimens such as the FLAG-Ida plus tyrosine kinase inhibitors [5]. As these patients are so rare, an appropriate diagnosis and the standard treatment for them are currently not available. Further studies are needed to answer the paradox of why inv(16)-associated AML has a relatively good prognosis, while its coexistence of the BCR-ABL1 in CML results in a rapidly progressive disease.

Declaration of Interest:

The authors of this manuscript declare that no one has a conflict of interest to disclose.

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