LETTER TO THE EDITOR
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Large and Multi-Nuclei Blasts in Hypotriploid Karyotype and TP53 Mutation Acute Myeloid Leukemia with P210 *BCR::ABL1* Transcript

Yihong Huangchuan, Xueyan Chen
Shenzhen Longhua District People's Hospital, Clinical Laboratory, Department of Clinical Laboratory, Shenzhen, P.R. China

Xueyan Chen, M.D., Shenzhen Longhua District People's Hospital, Clinical Laboratory, Department of Clinical Laboratory, Shenzhen, P.R. China
13632546963@163.com
https://orcid.org/0000-0002-5435-0888

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To the editor:

A 62-year-old woman with no significant past medical presented to the general practice clinic complaining of fatigue for two weeks. The doctor promptly referred her to the hematology department due to the initial complete blood count test indicating leukocytosis(20.8×10^9/L), anemia (hemoglobin 79g/L), and thrombocytopenia (7×10^9/L). Abdominal ultrasound did not reveal splenomegaly. The peripheral blood smear revealed 2% blasts and no basophils. Bone marrow cytology showed hypercellularity, with 12% myeloblasts and 31% large cells containing two or more nuclei(**Fig 1**). Leukemic cells were positive for CD34, HLA-DR, CD13, CD33, CD38, CD123, cMPO. These results confirmed that large cells were myeloblasts. Karyotyping analysis showed 46, XX, t(9;22)(q34; q11.2)[8]/60~65<3n>, XXX, -3, -4, -5, +6, -7, +8, -9, t(9;22)(q34;q11.2)×2, -10, +11, -12, +13, -16, -17, -18, +19, +20, +21, -22[cp5]/46, XX[7] (**Fig 1 J-K**). A comprehensive analysis of 20 karyotypes revealed the presence of three cell lines, two of which were abnormal.

P210 *BCR::ABL1* transcript was detected in bone marrow samples, revealing P210 *BCR::ABL1* /ABL1 100.0 and BCR-ABL P210 (%^{IS}) 29.4(**Fig 1 L**). Mutation analysis revealed a primary missense mutation in TP53, exon six c.584T>A p.I195N, with a variant abundance of 62.89%. The diagnosis was hypotriploid karyotype and TP53 mutation Acute Myeloid Leukemia with P210 *BCR::ABL1* transcript. After one round of the VA regimen (azacitidine 100 mg QD D1-7 combined with venetoclax 100 mg on D1, 20-300 mg on D2, and 40-300 mg on D3-7), along with imatinib 600 mg, the BCR-ABL (%^{IS}) decreased to 11% (**Fig 1 L**) and the PLT count increased to 51×10^9/L. After three weeks of continuous oral administration of imatinib 60mg tid, BCR-ABL (%^{IS}) declined to 5.6%(**Fig 1 L**); no TP53 gene mutation was detectable, and the chromosome analysis was consistent with the initial diagnosis. Bone marrow cytology showed hypercellularity with 22% myeloblasts. The patient resumed antitumor

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therapy with imatinib 600mg and venetoclax 100mg. This time, the patient was unable to tolerate chemotherapy, fell into a coma, and passed away three months later due to his family's decision to forgo further treatment.

In this case, the absence of antecedent leukocytosis, basophils, or splenomegaly supports a diagnosis of P210 *BCR::ABL1*-positive AML. Genetic risk stratification categorizes AML with *BCR::ABL1* fusion, complex karyotypes (such as triploidy), -5/5q, and -7/7q as having poor risk[**1**]. Blast cells and stem cells in AML require BCL-2 for survival, and preclinical studies have demonstrated the efficacy of the BCL-2 inhibitor venetoclax in treating AML[**2**]. Combining venetoclax and TKI may be especially beneficial for patients with ph+ clones predominate without other significant coexisting drivers[**3**]. One potential reason is that chromosomal instability can lead to the emergence of subclones harboring the Philadelphia chromosome in advanced leukemia, and TKI administration may not yield further advantages if *BCR::ABL1* fusion is not the primary oncogenic driver[**3**]. Unlike CML, *BCR::ABL1* fusion may confer a proliferative advantage in AML because it is unlikely to serve as the primary mutational driver[**4**]. Thus, the venetoclax and TKI combination regimen represents a feasible treatment option for ph+ myeloid leukemia, potentially presenting a particular advantage for patients with CML-bp due to its targeting of the primary driver, *BCR::ABL1* fusion[**3, 5**].

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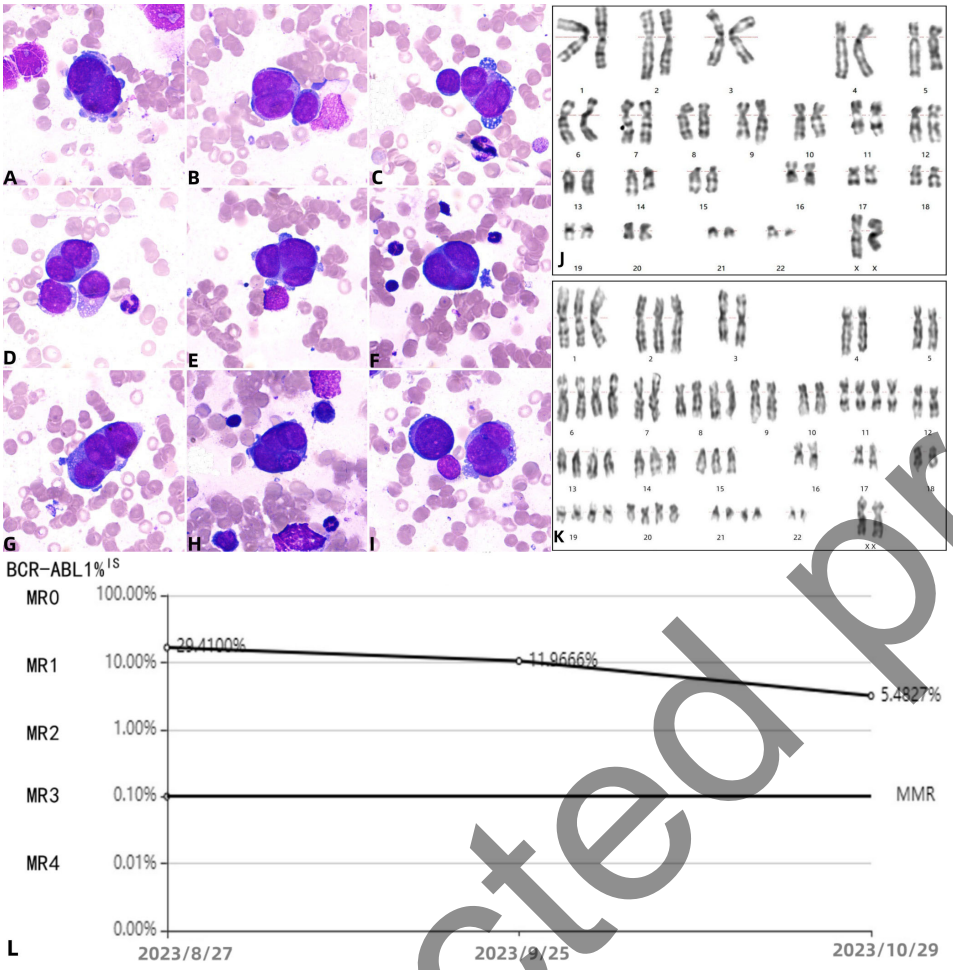

Figure 1. Bone marrow morphology and chromosome karyotype(**A-K**): the bone marrow aspirate showed binucleated leukemia cells (**A-D**) and multinucleated leukemia cells(**E-I**), with basophilic and vacuolated cytoplasm; Wright-Giemsa staining×1000; 8 cells showed translocation between chromosomes 9 and 22, with breakage and rejoining at 9q34 and 22q11.2, 46, XX,t(9;22)(q34;q11.2)[8] (**J**). The second abnormality, hypotriploid, involves multiple abnormalities in chromosome number. Specifically, there are two groups of T (9; 22) present, denoted as 60~65<3n>, XXX, -3, -4, -5, +6, -7, +8, -9, t (9; 22) (q34; q11.2) × 2, -10, +11, -12, +13, -16, -17, -18, +19, +20, +21, -22[cp5] (**K**). Change in BCR-ABL1 (%) during treatment(**L**).

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