LETTER TO THE EDITOR

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

Hipotriploid Karyotip ve P210 *BCR::ABL1* Transkripti ile *TP53* Mutasyonu Olan Akut Miyeloid Lösemide Büyük ve Çok Çekirdekli Blastlar

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To the Editor,

A 62-year-old woman with no significant past medical history presented to the general practice clinic complaining of fatigue for 2 weeks. The doctor promptly referred her to the hematology department due to the initial complete blood count test indicating leukocytosis ($20.8x10^9$/L), anemia (hemoglobin of 79 g/L), and thrombocytopenia ($7x10^9$/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 (Figures 1A-1I). Leukemic cells were positive for CD34, HLA-DR, CD13, CD33, CD38, CD123, and cMPO. These results confirmed that the 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] (Figures 1J and 1K). A comprehensive analysis of 20 karyotypes revealed the presence of three cell lines, two of which were abnormal.

The P210 *BCR::ABL1* transcript was detected in bone marrow samples, revealing P210 *BCR::ABL1*/ABL1 100.0 and BCR-ABL P210 ($\%^{IS}$) 29.4% (Figure 1L). Mutation analysis revealed a primary missense mutation in *TP53* at exon six of c.584T>A p.I195N, with a variant abundance of 62.89%. The diagnosis was acute myeloid leukemia (AML) with a hypotriploid karyotype and *TP53* mutation with the P210 *BCR::ABL1* transcript. After one round of the VA regimen (azacitidine at 100 mg daily on days 1-7 combined with venetoclax at 100 mg on day 1, 20-300 mg on day 2, and 40-300 mg on days 3-7) together with imatinib at 600 mg, the BCR-ABL ($\%^{IS}$) value decreased to 11% (Figure 1L) and the platelet count increased to $51x10^9$/L. After 3 weeks of continuous oral administration of imatinib at 60 mg three times daily, BCR-ABL ($\%^{IS}$) declined further to 5.6% (Figure 1L). 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 therapy with imatinib at 600 mg and venetoclax at 100 mg. This time, the patient was unable to tolerate chemotherapy, fell into a coma, and passed away 3 months later due to the family's decision to forgo further treatment.

In this case, the absence of antecedent leukocytosis, basophils, or splenomegaly supported 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 being of higher 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 tyrosine kinase inhibitors (TKIs) may be especially beneficial for patients with Philadelphia chromosome-positive clones predominating without other significant coexisting drivers [3]. One potential reason for this 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 chronic myeloid leukemia (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 is a feasible treatment option for Philadelphia chromosome-positive myeloid leukemia, potentially presenting a particular advantage for patients with CML of the blast phase due to its targeting of the primary driver, *BCR::ABL1* fusion [3,5].

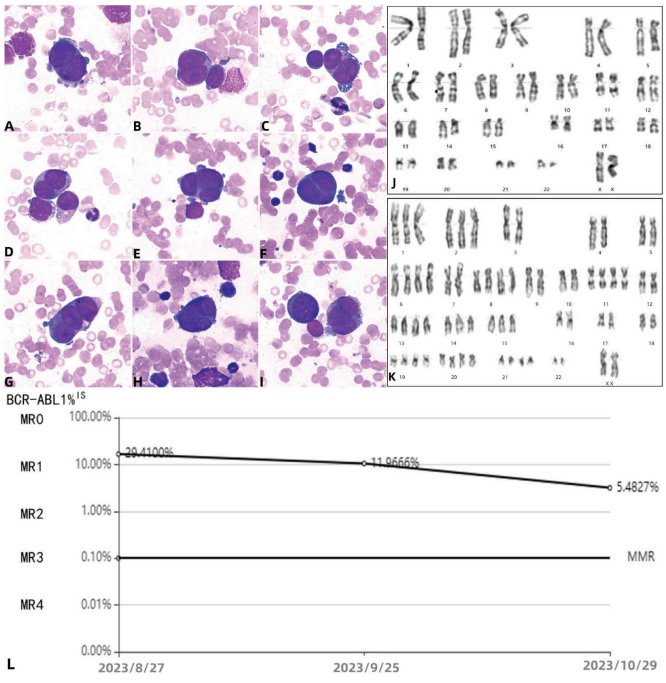

Figure 1. Bone marrow morphology and chromosome karyotype (A-K): the bone marrow aspirate showed binucleated leukemia cells (A-D) and multinucleated leukemia cells (E-I), with basophilic and vacuolated cytoplasm; Wright-Giemsa staining, 1000^{x}. Eight cells showed translocation between chromosomes 9 and 22, with breakage and rejoining at 9q34 and 22q11.2, 46,XX,t(9;22)(q34;q11.2)[8] (J). The second observed abnormality, hypotriploidy, 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). A change in *BCR-ABL1* % was achieved during treatment (L).

Keywords: Acute myeloid leukemia, P210 *BCR::ABL1* transcript, Hypotriploid karyotype

Anahtar Sözcükler: Akut miyeloid lösemi, P210 *BCR::ABL1* transkripti, Hipotriploid karyotip

Ethics

Informed Consent: Informed consent was obtained from the patient's family.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.H., X.C.; Concept: Y.H., X.C.; Design: Y.H., X.C.; Data Collection and Processing: Y.H., X.C.; Analysis or Interpretation: Y.H., X.C.; Literature Search: Y.H., X.C.; Writing: Y.H., X.C.

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