LETTER TO THE EDITOR

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A Case of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia with Coexistence of the *JAK2*V617F Clone

Philadelphia Kromozom Pozitif Akut Lenfoblastik Lösemi Olgusunda *JAK2*V617F Klon Birlikteliği

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To the Editor,

Essential thrombocythemia (ET) is a Philadelphia chromosome-negative myeloproliferative neoplasm. It usually presents with an indolent clinical course. Fewer than 5% of ET cases will transform into acute myeloid leukemia (AML). Studies have found that the probability of ET patients progressing to AML is 0.7%-3% in 10 years and 2.1%-5.3% in 15 years [1]. However, there are few reports to date about ET progressing to acute lymphoblastic leukemia (ALL). Alhuraiji et al. [2] reported four cases of ET that progressed to ALL, only one of which progressed to Philadelphia chromosome-positive ALL (Ph^+-ALL).

Our index case was a 56-year-old man with a large hematoma in the left scapular region and fever. Routine blood tests showed white blood cell (WBC) count of 16.31×10^9/L and platelet (PLT) count of 2716×10^9/L. Bone marrow (BM) examination showed marked proliferation of mature megakaryocytes (Figure 1A). Karyotype analysis showed 46,XY[20]. The quantitative polymerase chain reaction (qPCR) analysis for the *JAK2*V617F point mutation was positive and that for the *BCR::ABL1* fusion gene was negative. This case fulfilled the clinical criteria for the diagnosis of ET. The patient received hydroxyurea at 1.0 g twice daily and interferon-alpha (IFN-α) at 3 million IU twice weekly for 2 weeks, and his PLT count decreased to 839×10^9/L. Two months later, the patient discontinued treatment for unknown reasons and was lost to follow-up.

Three years later, the patient revisited our hospital with feelings of fatigue and dizziness. Routine blood tests showed WBC count of 100.42×10^9/L and PLT count of 20×10^9/L. BM examination showed hyperplasia of nucleated cells, blasts accounted for 81.5%, and 100% of these cells were peroxidase-negative (Figure 1A). The BM biopsy showed abundant blasts and no evidence of increased reticulin fibrosis (Figures 1B and 2). Flow cytometry testing revealed that 86.63% of BM blasts expressed HLA-DR, CD10, and CD19 (Figure 3). Karyotype analysis showed cytogenetic abnormalities with 46,XY,t(9;22)(q34;q11.2),add(14)(q32),del(20)(q13)×2[20] (Figure 4). The qPCR analysis for both the *JAK2*V617F point mutation and the *BCR::ABL1* fusion

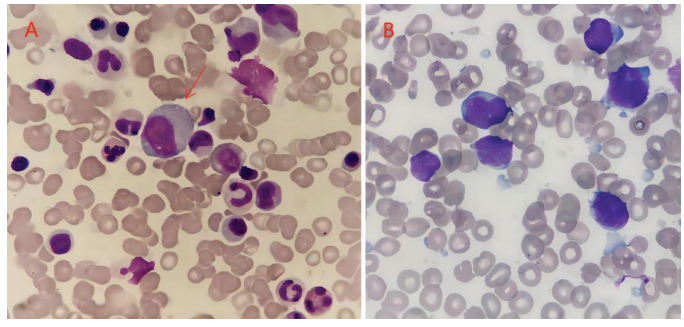

Figure 1. (A) Bone marrow morphology of essential thrombocythemia with increased and enlarged megakaryocytes, 100^x (red arrow). (B) Bone marrow morphology of acute lymphoblastic leukemia with a predominance of primitive and immature lymphocytes, 100^x.

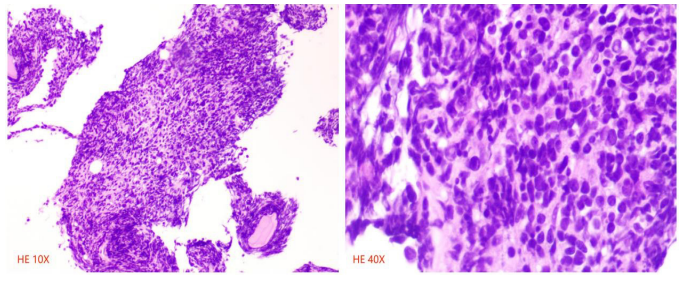

Figure 2. Bone marrow biopsy showed active proliferation of nucleated cells, blasts were diffusely proliferated, and there was no collagen fiber hyperplasia in the stroma.

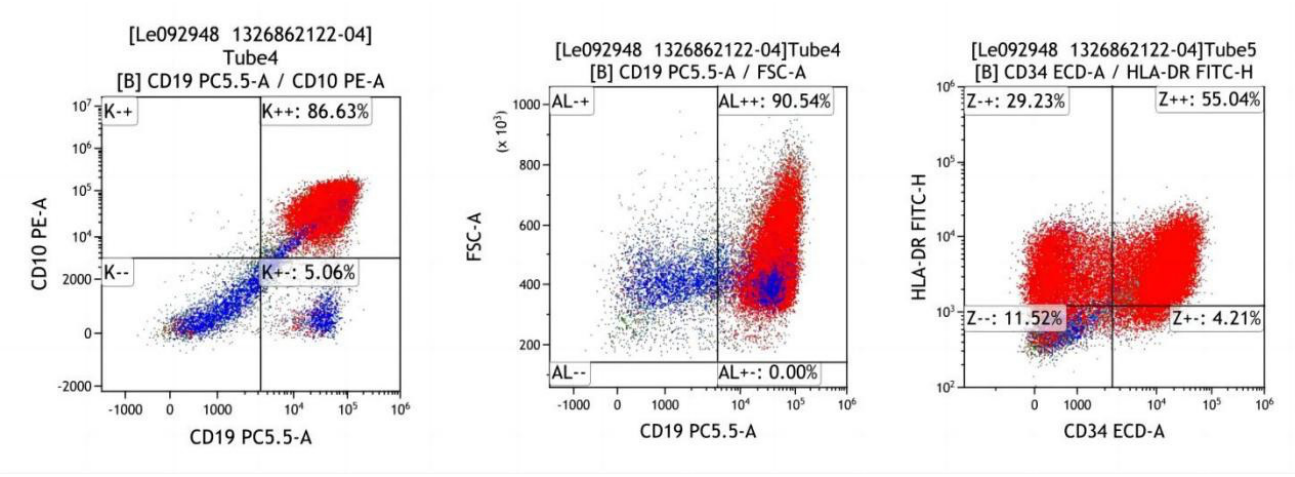

Figure 3. Immunophenotyping showed that 86.63% of the nuclear cells were blast cells expressing CD10, CD19, and HLA-DR, and some also expressed CD34.

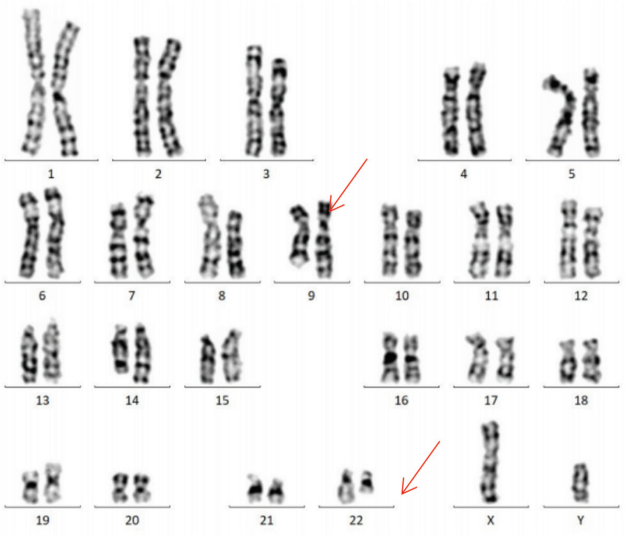

Figure 4. G-banded karyotype analysis showed 46,XY,t(9;22)(q34;q11.2),add(14)(q32),del(20)(q13)×2[20]. Red arrows indicate translocations on chromosomes 9 and 22.

gene (e1a2 transcript) was positive. The *JAK2*V617F missense mutation as detected by next-generation sequencing (NGS) was also positive (Figure 5). Based on the results of BM examination, Ph$^+$-ALL was diagnosed. The patient received imatinib at 600 mg once daily and the standard VDCP regimen consisting of vincristine, daunorubicin, cyclophosphamide, and prednisone. After primary induction therapy, BM assessment showed BM remission with 3% naive lymphocytes and the patient achieved minimal residual disease (MRD) negativity. Unexpectedly, the PLT count increased again to as high as 2419x10^9/L and the patient was unresponsive to hydroxyurea and imatinib. With two rounds of PLT apheresis and IFN-α at 5 million IU daily, the PLT counts gradually decreased to 300-400x10^9/L. Four more courses of consolidation chemotherapy were administered and imatinib was replaced with dasatinib at 70 mg once daily, aiming to sustain deep remission. The qPCR analysis for *BCR::ABL1* was negative after the first course of consolidation therapy. The patient remained MRD-negative after each chemotherapy

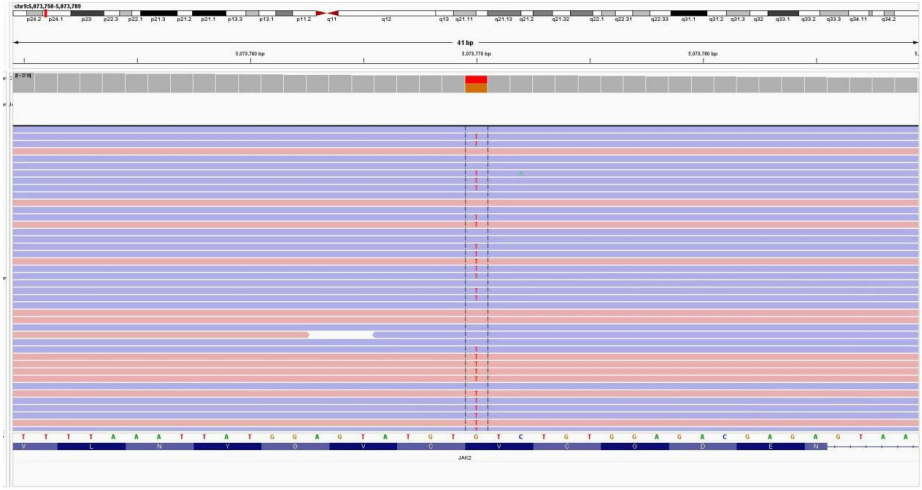

Figure 5. Next-generation sequencing results.

treatment. The karyotype returned to normal. The qPCR analysis for the *JAK2*V617F point mutation was always positive during ALL diagnosis and treatment, but the *JAK2*V617F missense mutation was negative as detected by NGS after the last chemotherapy treatment and there were no signs of extramedullary leukemia. The patient maintained major molecular response for 26 months after the diagnosis of Ph$^+$-ALL.

The *JAK2*V617F mutation can be detected in most cases of ET, and it is considered to be the driver mutation in these cases [3]. Only a small number of ET cases with the *JAK2*V617F mutation progress or transform to ALL; the majority of transformations are to AML [4]. There are some reports about ET cases with the *JAK2*V617F mutation progressing or transforming to lymphoid malignancies, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia, but fewer reports about ALL [2]. In our case, Ph$^+$-ALL was regarded as a second hematological neoplasm, reflecting disease progression rather than neoplastic transformation. The basis for this conclusion was that the *JAK2*V617F mutation and *BCR::ABL1* fusion gene coexisted at the time of the diagnosis of Ph$^+$-ALL, which suggests the existence of double clones. When the Ph$^+$-ALL entered molecular remission, the PLT count significantly increased again and the *JAK2*V617F mutation still existed. That further confirmed the above conclusion. In the literature, one study reported that treatment with IFN-α for ET has a high response rate [2]. For our patient, IFN-α was more effective in reducing PLTs compared to hydroxyurea, implying that the features of clinical presentation and the treatment response of ET were preserved during the leukemic phase.

Keywords: Essential thrombocythemia, *JAK2*V617F mutation, Acute lymphoblastic leukemia, Philadelphia chromosome-positive

Anahtar Sözcükler: Esansiyel trombositemi, *JAK2*V617F mutasyonu, Akut lenfoblastik lösemi, Philadelphia kromozom-pozitif

Ethics

Informed Consent: The patient provided written informed consent for use and publication of the clinical data.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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