Rare Case of Concomitant Polycythemia Vera and Chronic Lymphocytic Leukemia in a Young Male Patient

Genç Bir Erkek Hastada Polisitemia Vera ve Kronik Lenfositik Löseminin Nadir Birlikteliği

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To the Editor,

According to the 2016 classification of the World Health Organization, polycythemia vera (PV) is one of the Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPNs), characterized by the overproduction of red blood cells but not controlled by the mechanisms that generally regulate erythropoiesis [1], and the median patient age at diagnosis is 60 years. On the other hand, chronic lymphocytic leukemia (CLL), as the most common lymphoproliferative disorder (LPD), is a disorder of morphologically mature but immunologically incompetent B lymphocytes. The diagnosis of CLL is based on >5x10^9/L circulating mature B lymphocytes accompanied by the presence of a unique immunophenotype expressing CD5, CD23, CD43, and CD200 with weak expression of CD79b, FMC-7, CD20, and surface immunoglobulin [2]. Earlier studies suggested that cases of PV may precede or coincide with CLL; however, the pathobiology and mechanisms behind the development of these diseases in the same patient are still not fully understood [3]. In addition, it has been hypothesized that PV and CLL may originate from self-renewing hematopoietic stem cells (HSCs) with both lymphoid and myeloid potential [4,5,6,7]. Generally speaking, the concomitant presence of CLL and PV is rare and only a few such patients have been documented in the literature to date [8,9,10,11,12]. We noticed that almost all of these previously reported cases were cases of elderly patients. Herein, we describe the uncommon concurrence of PV and CLL in a 35-year-old male patient.

A 35-year-old man was referred to the hematology department, having presented with marked leukocytosis for 1 year and epigastric pain and diarrhea for 3 days. A complete blood count showed white blood cells of 39.8x10^9/L, platelets of 716x10^9/L, red blood cells of 6.9x10^{12}/L, and hemoglobin of 180 g/L with a hematocrit value of 59%. The circulating mature neutrophil and lymphocyte percentages were 60% and 38%, respectively, on a peripheral blood smear. The results of other laboratory investigations showed elevated levels of lactate dehydrogenase at 1232 U/L (normal reference range: 120-249 U/L) and β2-microglobulin at 3.69 mg/L (normal reference range: 1-3 mg/L), with low erythropoietin at 2.99 mIU/mL (normal reference range: 4.3-29 mIU/mL). Imaging examination showed hepatosplenomegaly and a small amount of effusion in the pelvic cavity, with enlargement of bilateral cervical lymph nodes, left supraclavicular lymph nodes, and bilateral inguinal and axillary lymph nodes. The peripheral blood smear revealed an increased number of typical small lymphocytes with spherical nuclei, soccer ball-like coarse chromatin and scanty cytoplasm, and marked thrombocytosis (Figure 1A). Bone marrow aspirate films showed hypercellularity with marked granulocytic proliferation, erythroid hyperplasia, and a significantly increased number of megakaryocytes, while mature lymphocytes were observed with similar morphologic features as in the blood (Figure 1B). Flow cytometric analysis suggested the diagnosis of CLL with 26.3% of CD5/CD19$^+$ cells displaying the following phenotype: CD20^{dim}, CD23$^+$, and FMC7$^-$, with kappa monoclonality (Figures 1C and 1D). Bone marrow cytogenetics revealed 46,XY[20]. Bone marrow biopsy also supported the diagnosis of PV, and the *JAK2V617F* mutation was verified by Sanger sequencing (Figure 1E). Next-generation sequencing was also performed and no significant pathogenic mutations were detected using a comprehensive multi-gene panel including *MYD88*, *SF3B1*, *TP53*, *NOTCH1*, *NOTCH2*, *BIRC3*, *CSF3R*, *U2AF1*, *ETNK1*, *PDGFRA*, *PDGFRB*, *SRSF2*, *SETBP1*, *JAK2*, *MPL*, and *CALR* mutations. *IGHV* genes were found to be mutated by polymerase chain reaction, but trisomy 12 was not detected by fluorescence in situ hybridization. In light of these findings, a diagnosis of concomitant PV and CLL was made. The patient was started on cytoreductive therapy with hydroxyurea (500 mg/day, three times per week) together with antiplatelet medications such as aspirin to prevent the occurrence of cardiovascular events. The patient is in good condition at present in follow-up and has not experienced any other thrombotic events, exhibiting significant clinical improvement during the course of treatment.

A study by Vannucchi et al. [13] reported that patients with previously diagnosed MPN may have increased risk of secondary LPD compared to the general population. The simultaneous existence of PV and CLL is uncommon. Several hypotheses have

been suggested to explain this rare finding. Some researchers hold the view that, despite clinical and biological diversity, the growing incidence of CLL in Ph-MPN patients reflects the existence of shared pathophysiological characteristics between these two distinct disorders by means of a common genetic link and the influence of the microenvironment [14]. However, other researchers argue that the concurrence of CLL and PV arises from separate HSCs. In other words, the emergence and progression of myeloid and lymphoid neoplasms occur independently. Several recent publications revealed that concomitant *JAK2V617F*-positive PV and CLL in the same patient originated from distinctly separate HSCs [12].

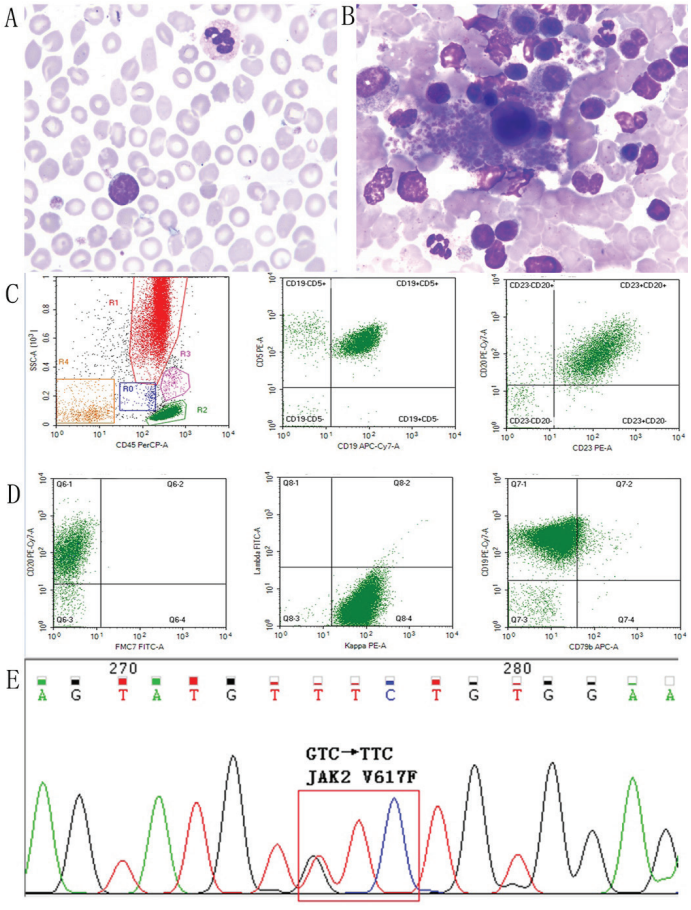

Figure 1. Peripheral blood smear revealed an increased number of typical small lymphocytes with spherical nuclei, soccer ball-like coarse chromatin and scanty cytoplasm, and marked thrombocytosis (A, Wright-Giemsa, 1000^{x}). Bone marrow aspirate showed hypercellularity with marked granulocytic proliferation, erythroid hyperplasia, and a significantly increased number of megakaryocytes while mature lymphocytes were observed with morphological features similar to those of the peripheral blood (B, Wright-Giemsa, 1000^{x}). Flow cytometric analysis suggested the diagnosis of chronic lymphocytic leukemia with 26.3% of CD5/CD19+ cells displaying the following phenotype: CD20dim, CD23+, and FMC7-, with kappa monoclonality (green dots) (**C, D**). The JAK2V617F mutation was verified by Sanger sequencing (**E**).

In summary, we have described a relatively young male patient with the diagnosis of concomitant PV and CLL. However, the question of whether this concomitant situation indicates a common origin requires further study. A variety of assumptions have been considered to explain this rare event, and according to recent studies, concomitant PV and CLL may represent two distinct progenitors of myeloid and lymphoid lineage.

Keywords: Polycythemia vera, Chronic lymphocytic leukemia, Concurrence, immunophenotype

Anahtar Sözcükler: Polisitemia vera, Kronik lenfositik lösemi, Eşzamanlılık, İmmünofenotip

Ethics

Ethics Committee Approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the relevant institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from this patient.

Authorship Contributions

Concept: Y.Z., T.L.; Design: Y.Z., T.L.; Data Collection or Processing: Y.Z., T.L.; Analysis or Interpretation: Y.Z., T.L.; Literature Search: Y.Z., T.L.; Writing: Y.Z., T.L.

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