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## Simultaneous presentation of *JAK2* V617F mutation-related essential thrombocythemia and B-cell chronic lymphocytic leukemia

**TO THE EDITOR:** The simultaneous development of *JAK2* mutation-related essential thrombocythemia and B-cell CLL is very rare in the context of contemporary myeloid and lymphoid malignancies—until 2012, only 8 such cases had been reported. Moreover, the myeloproliferative neoplasm lymphoid/plasmacytoid association has not been evaluated in a systematic scientific manner, and therefore, the pathogenesis of this condition remains unclear. We emphasize that further studies are needed to understand the pathophysiology underlying the simultaneous development of these two diseases that have markedly different clinical, prognostic, and therapeutic characteristics.

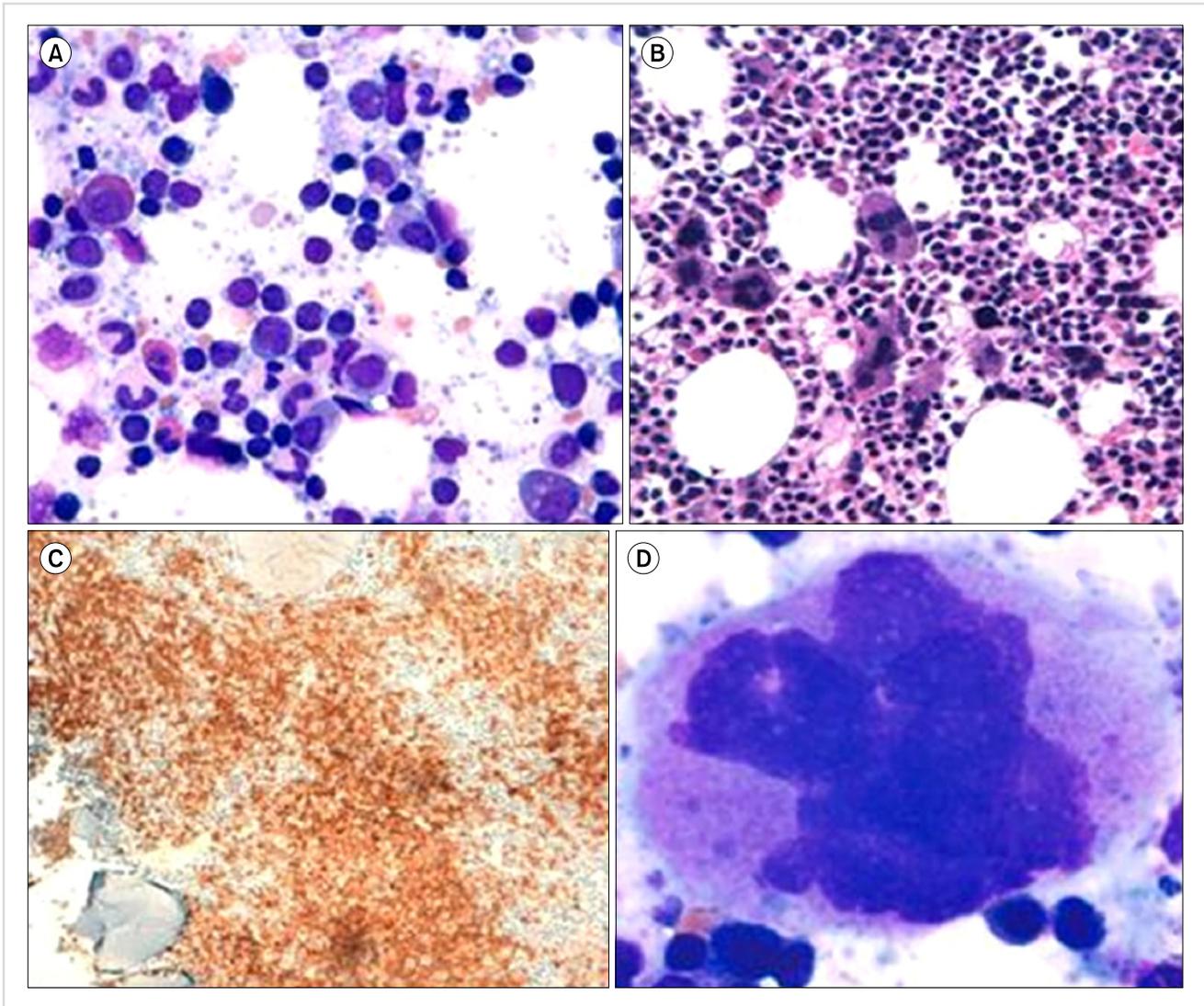
A case of simultaneous development of polycythemia vera and CLL was first reported in 1953 [1]. In certain hematological malignancies, the involvement of two different cell lineages is possible, such as in the case of chronic myeloid leukemia in the blast crisis phase, which can evolve into acute lymphoblastic leukemia. Furthermore, in mastocytosis, although rare, more than 30% of cases show an association with myeloproliferative neoplasm (MPN) and/or myelodysplastic syndrome (MDS) [2]. The coexistence of CLL or lymphoma with a solid neoplasm, such as prostatic or

intestinal cancer, has also been reported. However, the simultaneous development of Philadelphia-negative (Ph-) MPN and CLL is uncommon.

We report the case of a 67-year-old Caucasian woman, who presented with leukocytosis (WBC count:  $20 \times 10^9/L$ ), lymphocytosis (lymphocytes: 59%; absolute lymphocytes:  $11.8 \times 10^9/L$ ), and thrombocytosis (platelet count:  $725 \times 10^9/L$ ). She had no significant previous illnesses. She worked as a ceramist and led a healthy lifestyle, involving regular physical activity; she had a normal body mass index and did not smoke. The physical examination indicated normal findings, and revealed no superficial lymphadenopathy. Abdominal ultrasonography and chest radiography also showed no evidence of lymphadenopathy and/or organomegaly. Examination of the bone marrow aspirate (Fig. 1A), as well as the bone marrow biopsy specimen, showed more than 30% infiltration; the cells mainly comprised small lymphocytes with scant cytoplasm in the interstitial and paratrabecular regions (Fig. 1B). On immunohistochemical analysis, the lymphoid immunophenotype showed antigenic positivity for CD5 (Fig. 1C), CD20, CD23, and CD79a, whereas zeta-chain-associated protein kinase 70 (ZAP-70) assay yielded negative results. Megakaryocytosis was also noted, with large dysplastic megakaryocytes with hyperlobated nuclei (Fig. 1D), megakaryocytes with naked nuclei, and micromegakaryocytes. Bone marrow fibrosis was not present.

In both the bone marrow aspirate and the peripheral blood samples analyzed by using flow cytometry, we identified a lymphoid population of CD19+, CD5+, CD20+, and CD23+ cells with clonal restriction for the “kappa” light chain, belonging to the IgD surface immunoglobulins. Based on the exclusion criteria, “monoclonal B-cell lymphocytosis” was ruled out [3]. Given the morphological characteristics of the megakaryocytes, as well as the thrombocytosis, we tested for the *JAK2* mutation, and its presence was confirmed. We did not assess the clonality of the *JAK2* mutation in the sorted CD5+/CD19+ CLL cells. In the peripheral blood, fluorescence *in situ* hybridization indicated negative results for *BCR/ABL* translocation.

The diagnostic criteria were suggestive of simultaneous myeloid and lymphoid lineage involvements, which represented the simultaneous presence of two neoplastic diseases—a *JAK2* mutation-related essential thrombocythemia (ET) and a B-cell CLL. Regarding the myeloid involvement, taking into account the patient’s high-risk stratification (age > 60 years, even if the patient has no clinical history of thromboembolic or cardiovascular disease), we started the patient on cytoreductive therapy with hydroxyurea (500 mg/day) plus low-dose aspirin [4]. Instead, for the simultaneous lymphoid involvement, considered to be a CLL Binet stage A, without comorbidities, we adopted a “wait and watch” approach. The first follow-up after diagnosis showed that the patient’s platelets had decreased to  $400 \times 10^9/L$ , and her lymphocytosis persisted without aggravated leukocytosis. The physical examination revealed no enlarged lymph



**Fig. 1.** (A) Bone marrow aspirate (May-Grünwald-Giemsa, MGG) showing lymphoid hyperplasia represented by small cells with scant cytoplasm (magnification 400×); (B) Bone marrow biopsy (hematoxylin-eosin) showing lymphoid hyperplasia and simultaneous megakaryocytic hyperplasia, isolated and in groups (magnification 200×); (C) Bone marrow biopsy showing a population of small lymphoid cells that were CD5+ (magnification 200×); and (D) Bone marrow aspirate (MGG) showing large megakaryocyte with hyperlobated nucleus (magnification 1,000×).

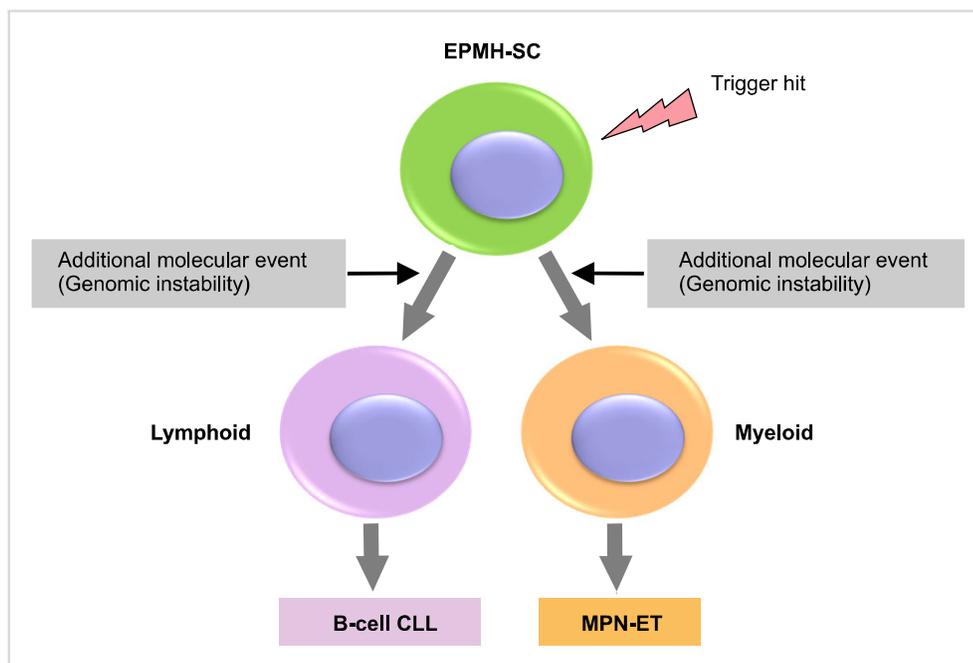
nodes. The patient will carry out scheduled checks regularly.

The simultaneous presence of ET with B-cell CLL is a rare event in the context of simultaneous myeloid and lymphoid malignancies. The MPN-lymphoid combination is uncommon, and it is generally characterized by the coexistence of a Ph- MPN and B-cell CLL. The simultaneous presence of chronic myeloid and lymphoid/plasmacytoid neoplastic disease occurs in  $\leq 1\%$  of patients [5]. Generally, the two diseases have been reported to occur independently from one another at different time points. However, cases of coexisting ET and CLL are occasionally reported, with only 8 cases described prior to 2012 [6].

In MPN with lymphoproliferative disease (LPD), a pathogenic factor has not yet been identified. The combination of MPN and LPD may in fact be the clinical manifestation

of two unrelated diseases that coexist by chance. According to Tabaczewski [7], in cases of coexisting MPN and CLL, a "trigger hit" occurs in an early progenitor cell, which then differentiates into both lymphoid and myeloid cells. Subsequently, additional molecular events that generate genomic instability may occur during lymphoid and myeloid neoplastic differentiation, resulting in the development of two diseases that have the same origin but arise from different cellular lines (Fig. 2).

The *JAK2* mutation in MPN is acquired and is not a germline mutation. However, because the *JAK2* mutation is not the trigger event, and because it correlates with a single phenotype, the putative link between MPN and LPD is not specific [8]. Nevertheless, the *JAK2* mutation allelic burden seems to be a significant factor that increases the



**Fig. 2.** Pathogenetic hypothesis of the simultaneous presence of myeloid and lymphoid disease. Abbreviation: EPMH-SC, early progenitor multipotential hematopoietic stem cell.

risk of developing a lymphoid malignancy by 12 times in patients with Ph- MPN [9]. Furthermore, a link exists between the activation of Janus Kinases 1, 2, and 3 and the “Ikaros” family of transcription factors, which are also involved in the development of lymphomatous malignancies that are typically associated with a poor outcome [10, 11].

The immature B-cell marker ZAP-70 is expressed in approximately 30% of CLL cases and is an indicator of poor prognosis, along with unmutated immunoglobulin gene status. In most of the cases of MPN coexisting with CLL reported thus far, the CLL phenotype showed positivity for ZAP-70; however, the present case indicated negative results for ZAP-70.

In ET with CLL, the presence of the *JAK2* mutation within the lymphoid cells is variable or, in most cases, not detectable. An evaluation comparing the ZAP-70 and *JAK2* mutation profiles could help us understand the reasons for this finding [12]. In addition, the technical difficulty of preparing the lymphoid compartment of neoplastic lymphocytes for testing could be a significant reason why the *JAK* mutation in lymphoid cells is not detected in some cases [8].

We believe that further studies are needed to understand the pathophysiology that leads to the simultaneous presence of two diseases that have distinctly different clinical, prognostic, and therapeutic characteristics.

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#### Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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