Coexistence of chronic lymphocytic leukaemia and polycythemia vera

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SUMMARY

We report a rare case of coexistence of chronic lymphocytic leukaemia (CLL) and polycythemia vera (PV) in a patient initially diagnosed and treated for CLL. A 61-year-old man presented with fatigue and night sweats, with laboratory tests showing elevated haemoglobin, hematocrit (HCT), leukocyte count and splenomegaly. Peripheral blood smear revealed lymphocytosis with basket cells, and flow cytometry confirmed CLL (RAI stage II). FISH analysis was negative for del13q, del11q, trisomy 12, del 17p and del6q. Chemotherapy was started because of B symptoms. Persistent splenomegaly and elevated HCT at follow-up prompted further evaluation, which revealed a JAK2 V617F mutation and an erythropoietin (EPO) level <1 mIU/mL, confirming PV. The patient achieved remission for CLL, but required hydroxyurea and acetylsalicylic acid for PV. The coexistence of CLL and PV is rare and the underlying mechanisms are not well understood, although a common clonal haematopoietic stem cell origin or germline mutations are possible explanations. Although chemotherapeutic agents are known to induce PV, the elevated HCT at the time of CLL diagnosis suggests a pre-existing relationship between the two diseases. Therefore, elevated HCT in CLL patients should prompt consideration of PV.

Keywords: *Chronic lymphocytic leukaemia, Polycythemia vera, JAK2 V617F mutation, germline mutations*

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INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is defined as a low-grade lymphoproliferative neoplasm (LPN) characterised by $\geq 5 \times 10^9$/L clonal B cells expressing CD5, CD19, CD20(dim) and CD23 in the peripheral circulation (1). The disease is usually diagnosed at an advanced age, with a median age at diagnosis of 70 years. Clinical features include constitutional symptoms such as fever, weight loss and night sweats, enlarged lymph nodes, autoimmune complications or findings of immunodeficiency.

PV is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) in which the *JAK2* mutation is frequently observed (1). The median age at diagnosis is 60 years, and the diagnosis is usually made after an incidental haemoglobin elevation. In addition to hypertension, pruritus and vasomotor symptoms, complications such as thrombosis or haemorrhage may be observed.

The coexistence of LPN and MPN is very rare. It has been reported that lymphoproliferative disorders are more common in MPN patients (2). Whether these two clonal disorders are due to genomic instability or a fundamental genetic alteration that increases susceptibility to other clonal disorders, or whether they are purely coincidental, remains to be investigated. The *JAK2 V617F* mutation, which is found in a large proportion of MPN patients, has been associated with an increased risk of LPN (3). In addition, it is not clear whether drugs used to treat lymphoproliferative disorders also contribute to the development of MPNs (4).

To contribute to the literature, we present our patient who was treated for CLL and diagnosed with PV at follow-up and started treatment.

CASE

A 61-year-old male patient presented to our outpatient clinic with excessive fatigue and night sweats. His detailed medical history was unremarkable. On physical examination, the spleen was palpated 4 fingers below the rib. Laboratory tests showed haemoglobin 15.1 g/dL, HCT 46%, leukocyte count 231×10^9/L and platelet count 251×10^9/L. The peripheral smear showed lymphocytosis consisting of small mature lymphocytes and basket cells. Ultrasonography showed an enlarged spleen (175 mm). In addition, enlarged lymph nodes with thick cortex of various sizes were observed in the cervical axillary and inguinal areas (right axillary 17x5 mm, left axillary 19x6 mm, left lower cervical 6.6x5.6 mm and both inguinal 13x4 mm right and 9x4.5 mm left). The flow cytometric analysis of peripheral blood showed CD20 60%, CD5 80%, CD5+19 59% and CD23 52% (Figure 1).

Based on these findings, the patient was diagnosed with RAI stage 2 CLL. Genetic testing by FISH (del13q, del11q, trisomy 12, del 17p and del6q) was negative. The patient received 6 cycles of rituximab-bendamustine chemotherapy for B symptoms. A complete response was achieved in the parameters defining the function of the haematopoietic system. A complete response was achieved in the lymph nodes, which represent the tumour burden, but the spleen remained larger than 13 cm. Bone marrow biopsy showed hypercellularity and markedly increased proliferation in the erythroid series. There was no lymphoid infiltration and no increase in reticulin fibres. The HCT gradually increased (>55%) and hemoglobin exceeded 17.5 g/dL during follow-up without treatment. The EPO level was <1 mIU/mL and the *JAK2 V617F* mutation was found to be positive (Figure 2). Based on the haemoglobin elevation and the data obtained, we diagnosed PV according to WHO diagnostic criteria. We started treatment with acetylsalicylic acid and hydroxyurea. Informed consent and permission to publish the case report was obtained from the patient.

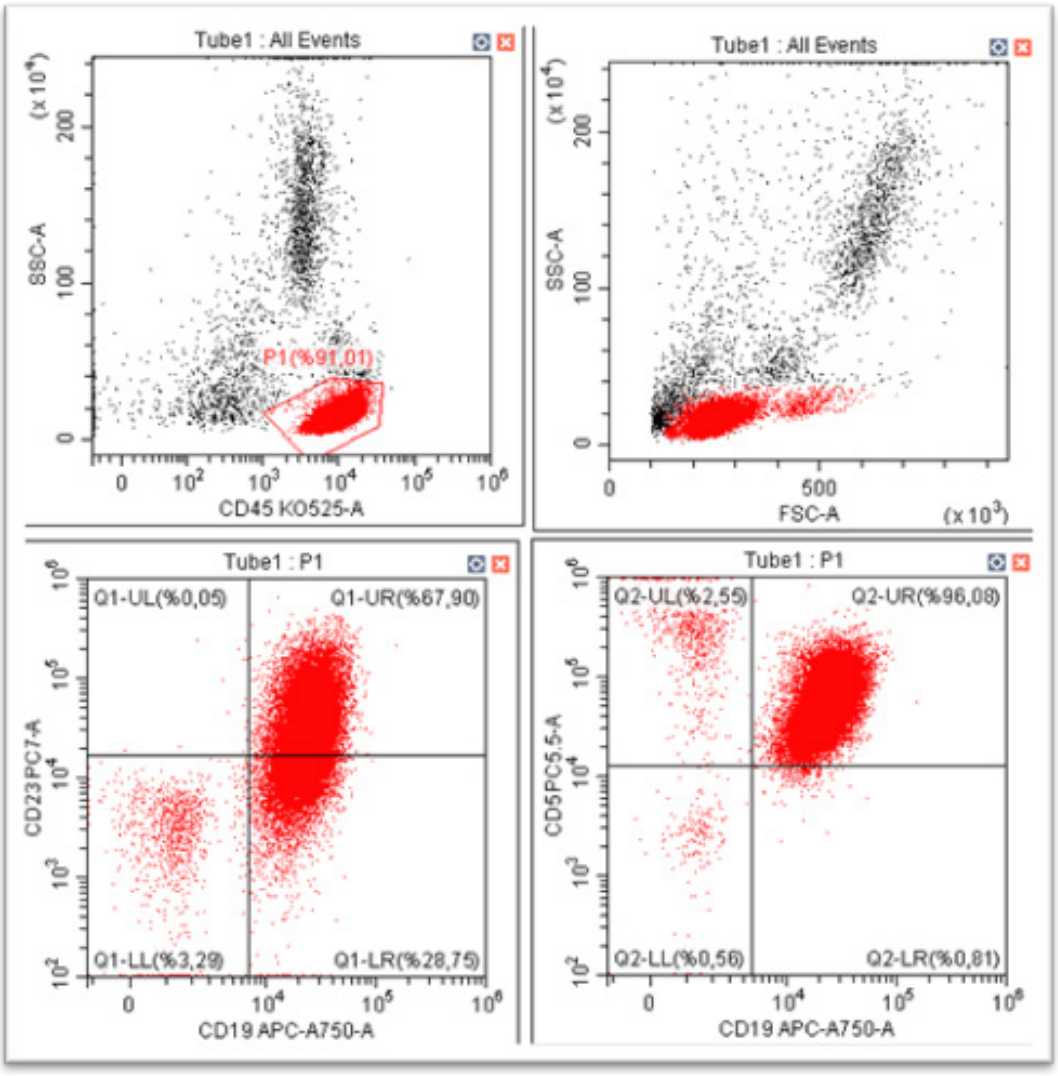

Figure 1. Immunophenotypic characterization of clonal B-cells.Gated CD19+ lymphocytes show co-expression of CD5 in 80% and CD23 in 52% of cells. Dual CD5+CD19+ expression is seen in 59% of lymphocytes. CD20 is expressed in 60% of the clonal population. This immunophenotypic pattern is consistent with a diagnosis of chronic lymphocytic leukemia (CLL).

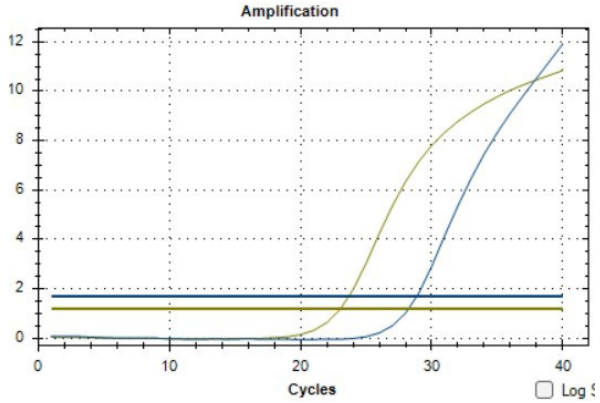

Figure 2. This image shows a real-time PCR (qPCR) amplification curve for the detection of the *JAK2 V617F* mutation. The x-axis represents the number of PCR cycles, while the y-axis indicates the fluorescence signal intensity reflecting DNA amplification. Two amplification curves are observed: one in blue and the other in green/yellow. These curves likely represent the patient sample and either a positive or negative control. Both curves cross the threshold between approximately cycle 22 and 28, indicating the presence of amplified target DNA. This pattern confirms a positive *JAK2 V617F* mutation result, which is a major diagnostic criterion for polycythemia vera according to WHO guidelines.

DISCUSSION

The *JAK2 V617F* mutation is a gain-of-function mutation and is a genetic alteration that is detected in >95% of PV and is one of the main diagnostic criteria (2). In addition, a comprehensive analysis of 3700 patients in China showed that the *JAK2 V617F* mutation was observed in the peripheral blood of approximately 1% of healthy individuals (5). *JAK2* mutations are most commonly found in erythroid and myeloid cells. Their presence in B lymphocytes, T lymphocytes and NK cells is controversial (6). The possible contribution of germline mutations such as *DDX41, RUNX1, ETV6, ANKRD26* and *POT1*, which are associated with the occurrence of both myeloid and lymphoid neoplasms, has been mentioned in the coexistence of MPN and LPN (7). It has not been definitively shown that these two disease groups originate from a common haematopoietic stem cell. It has been observed that patients with MPN have a higher risk of developing lymphoproliferative diseases compared to the general population (3). In the GIMEMA group study, 46 patients with CLL and concomitant MPN were retrospectively evaluated. 10 patients had PV with CLL. The investigators reported that the rate of co-existence of CLL and MPN was 1%. In this study, it was highlighted that 82% of the patients were early stage and did not require treatment (8). Another study included 877 patients with MPN and found that 4.5% developed secondary lymphoproliferative disorders. It was also reported that this risk was even higher in patients with the *JAK2V617F* mutation, with a 12-fold increased risk of developing CLL (2). Studies have provided information on which disease is detected first in the association of these two diseases. In a case series of 44 patients with a coexistence of MPN and LPN, the two diseases were detected simultaneously in 32% of the patients, while the myeloid disease was detected before the LPN in 52% of the cases (median 37 months later) and the LPN before the myeloid neoplasm in 16% of the cases (median 41 months later). Considering the high haemoglobin and HTC despite splenomegaly at the time of CLL diagnosis in our patient, it would be correct to assume that both diseases were concurrent. The most common LPN was non-Hodgkin's lymphoma (50%), followed by CLL (27%). The *JAK2V617F* mutation was detected in 30 cases (79%) (9).

Regarding the triggering of other underlying disease groups by drugs, it has been observed that myeloproliferative disease can develop both in CLL patients treated with cytotoxic chemotherapy or radiotherapy and in CLL patients followed without treatment (4). In the treatment of MPN, there is a study mentioning the mutagenic potential of hydroxyurea, which is thought to contribute to an increase in the incidence of CLL (10). We do not believe that our patient had a drug-related MPN. In our case, there were laboratory findings suggesting the presence of MPNs along with the diagnosis of CLL, and there was a short interval between CLL treatment and MPN diagnosis.

In conclusion, we believe that it should be kept in mind that LPN and MPN may be associated at the beginning or may follow each other in the process and this should be taken into consideration in the follow-up of patients.

Conflict of interests: The authors declare no conflicts of interests.

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