

# A Rare Case of Chronic Lymphocytic Leukemia in A Patient With Essential Thrombocythemia

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## Abstract

Essential thrombocythemia (ET) and chronic lymphocytic leukemia (CLL) are 2 distinct, clonal hematologic malignancies. The association of ET and CLL is very rare, and only a handful of cases have been described in the literature, the pathogenic mechanisms of this phenomenon remain unclear. Here we describe a patient with an uncommon case of Janus Kinase 2 (JAK2) V617F positive ET treated by hydroxyurea and pipobroman, who eventually developed a second unrelated hematologic malignancy, CLL.

**Key words:** Essential thrombocythemia, chronic lymphocytic leukaemia.

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## INTRODUCTION

Essential thrombocythemia (ET) and chronic lymphocytic leukemia (CLL) are 2 distinct, clonal hematologic malignancies. The World Health Organization classification of tumors of hematopoietic and lymphoid tissues defines ET as one of the Philadelphia-negative classical myeloproliferative neoplasms [1,2], and CLL as a low grade lymphoproliferative neoplasm with  $\geq 5 \times 10^9/l$  clonal B-cells in the peripheral circulation that express CD5, CD19, dimCD20, and CD23 [1].

The association of ET and CLL is very rare, and only a handful of cases have been described in the literature, the pathogenic mechanisms of this phenomenon remain unclear. Here, we present a patient with a diagnosis of ET who developed CLL 12 years after his initial diagnosis.

## CASE REPORT

A platelet count of  $697 \times 10^9/l$  was detected in this 52 year-old man in 2004 during his yearly medical checkup. Other blood findings were: Hb 14.3 g/dl ; WBC  $11.7 \times 10^9/l$ , with  $7.7 \times 10^9/l$  neutrophils and  $2.8 \times 10^9/l$  lymphocytes. He was completely asymptomatic and had no significant past medical history. In particular, he denied any bleeding, easy bruising, or gastrointestinal symptoms. Physical examination was unremarkable, there was no lymphadenopathy, liver and spleen were not enlarged. Abdominal ultrasound scan was normal.

Prothrombin time, activated partial thromboplastin time, and fibrinogen were normal. Peripheral blood examination showed microcytosis, normal platelet morphology, and normal differential leukocyte count. After confirming persistent thrombocytosis on peripheral blood smear review, our diagnostic evaluation focused on determining whether this process was reactive or clonal. C-Reactive Protein CRP and other acute phase reactants were evaluated, results were within normal ranges. Ferritin level was normal (60 ng/ml). Serum biochemical parameters were normal

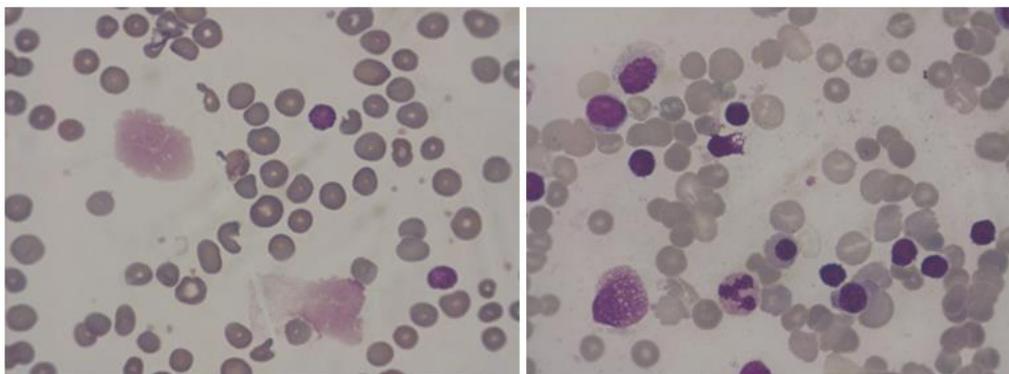
Bone marrow examination showed megakaryocytic hyperplasia with some abnormal forms, and several platelet clumps in the absence of significant fibrosis. Erythroid and granulocytic precursor cells were increased. Allele-specific polymerase chain reaction (PCR) method revealed the presence of Janus Kinase 2 (JAK2) V617 mutation, which was estimated at 22.5% of JAK2 alleles. A diagnosis of ET was established.

Our patient was started on hydroxyurea 1 g/day in association with antiplatelet therapy (Aspirin : 250mg/daily). This treatment allowed maintaining a good platelet count control. Hydroxyurea was discontinued 6 years after initiation of treatment due to increased platelet count and the patient started pipobroman 50mg daily, which performed to maintain a normal blood platelet count.

In 2016, the patient was noted to have an increased WBC of  $14 \times 10^9/l$  with 39% granulocytes,

33% lymphocytes, and an absolute lymphocyte count of  $4.6 \times 10^9/l$ . Hematocrit and hemoglobin at that time were 45.7% and 14.9 g/dl respectively, and the platelet count was  $334 \times 10^9/l$ . A peripheral blood smear showed leukocytosis with a predominance of small, well-differentiated lymphocytes (figure 1). Flow cytofluorometric analysis of peripheral blood

lymphocytes was consistent with a B-lymphocyte chronic proliferation with monoclonal kappa light chain restriction (CD3 20%, CD19 74%, CD19-CD5 99%, CD23 99% ,kappa chain 97%, lambda chain 3%, CD11c 93%, FMC7 40%). A CLL, stage A of Binet Staging System, was diagnosed and no further treatment was advised.



**Fig-1. Peripheral blood smear showing mature small lymphocytes with scanty cytoplasm, some smear cells (Gumprecht's shadows) are also visible. May-Grunwald Giemsa.  $\times 1000$ .**

He received close follow-up, and his last WBC in 2019 was  $13.5 \times 10^9/l$  with 32% granulocytes, 61% lymphocytes (absolute lymphocyte count of  $8.2 \times 10^9/l$ ), and a platelet count of  $385 \times 10^9/l$ .

## DISCUSSION

ET is an acquired myeloproliferative disorder characterized by a sustained elevation in the platelet count with a tendency for thrombotic and hemorrhagic events during its clinical course [3, 4]. An elevated platelet count is related to an expansion of the megakaryocytic lineage, the disorder is usually considered to be a clonal disease arising in a multipotent stem cell. CLL is also the result of a neoplastic clonal expansion, characterized by a progressive accumulation of small, mature-appearing lymphocytes in the blood, bone marrow and lymphoid organs [5]. The origin of tumor cells in CLL is unknown and, based on their phenotypic characteristics several hypotheses have been formulated in the last few years. These cells can be linked to the B1 lineage found in a mouse model expressing the Ly1/CD5 antigen [6], but they are also phenotypically close to naive B cells, mature B cells, and memory B cells [7-10]. Another way to classify CLL cells is related to their functional properties since several functional and phenotypic characteristics resemble the recently described B10 cell subset [11].

JAK2 V617F positive ET and CLL are 2 distinct, clonal hematologic malignancies. There are very few cases of co-existent CLL and ET reported in the literature [12-13]. The etiology of this co-occurrence could be multifold. A pre-JAK2 pluripotent stem cell mutation leading to genetic instability and susceptibility to further genetic alterations after lineage

differentiation is a possibility [14]. A change in the bone marrow environment caused by the MPN could result in alterations of various cytokines that have fibrogenic, osteogenic, angiogenic, and leukemogenic potential [15]. By a combination of magnetic cell sorting and fluorescent in situ hybridization (FISH), Reeder and colleagues demonstrated the possibility of clonal involvement of both the B and T lymphocytes in primary myelofibrosis. This has not been studied in other MPNs, but it is a possible mechanism [16]. These could also occur purely by chance.

Rare, co-occurring, unrelated hematologic malignancies provide a diagnostic challenge. Patients with MPNs usually present with leukocytosis due to myeloid proliferation, and a concurrent lymphocytosis due to CLL can be easily missed. This paper describes a patient with a diagnosis of JAK2 V617F positive ET who developed CLL 12 years after his initial diagnosis.

## CONCLUSION

There is still confusion whether myelo- and lymphoproliferative disorders originate from the same cell or there are distinct entities coexisting or following one another. Further studies are required to provide a more complete understanding of the association between CLL and myeloproliferative disorders.

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