

# Concomitant myeloproliferative and lymphoproliferative neoplasms, distinct progenitors: A case report and review of the literature

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**Abstract.** Patients with a Philadelphia chromosome-negative myeloproliferative neoplasm may develop a lymphoproliferative disorder; however, the clinical and molecular determinants and the chronological onset of the two events remain unknown. We herein report the case of a 64-year-old man with concomitant diagnosis of high-risk essential thrombocythemia with evidence of a thrombotic event and high-count monoclonal B-cell lymphocytosis (high-count MBL). The patient harbored a *JAK2V617F* mutation and one of the most common genetic alterations found in chronic lymphocytic leukemia (CLL) (del 13q), which may represent a sign of disease progression. He was initiated on cytoreductive therapy with hydroxyurea 500 mg 3 times per week and hypocoagulation treatment, and is currently under regular surveillance of MBL without CLL criteria.

## Introduction

The coexistence of myeloproliferative neoplasms (MPN) and lymphoproliferative neoplasms (LPN) is a rare finding. In particular, essential thrombocythemia (ET) and chronic

lymphocytic leukemia (CLL) rarely coexist in the same patient. Patients with a Philadelphia chromosome (Ph)-negative MPN may develop a lymphoproliferative disorder (LPD); however, the clinical and molecular determinants and the chronological onset of the two events remains unknown (1).

Monoclonal B lymphocytosis (MBL) is defined as the presence of a clonal B-cell population in the peripheral blood of  $<5 \times 10^9/l$  and no other signs of an LPD. Based on the number of clonal B cells, MBL is divided into 'low-count' ( $<0.5 \times 10^9/l$ ) and 'high-count' MBL ( $>0.5 \times 10^9/l$ ). MBL that precedes CLL, has a similar immunophenotype. It has been demonstrated that the natural history of CLL is preceded by MBL; however, despite its prevalence of 12% in the healthy population, MBL progresses to overt CLL/small lymphocytic lymphoma (SLL) in only 1-2% of the cases annually (2,3).

CLL/SLL is a disorder of morphologically mature but immunologically incompetent B lymphocytes. It is defined as  $>5 \times 10^3/\mu l$  circulating B lymphocytes with a specific phenotype expressing CD19, CD5, CD23, CD43 and CD200, and a weak expression of CD20, CD79b and surface immunoglobulin (4). Key pathways promoting CLL cell proliferation and survival are activation of B-cell receptor and nuclear factor- $\kappa B$  pathways (5). CLL, a mature B-cell neoplasm, represents one of the most frequent LPNs, and the most common type of leukemia in the elderly (6).

MPNs are known to be clonal hematopoietic stem cell diseases characterized by overproduction of one or more blood cell lines, albeit with normal maturation and hematopoiesis. MPNs represent a group of heterogeneous chronic conditions, in which the main picture is characterized by medullary proliferation of at least one myeloid lineage, and increased number of mostly mature elements in the peripheral blood (7).

According to the literature, concurrent manifestation of two chronic-stage myeloid and lymphoid neoplasms in the same patient is a rare condition that appears to account for

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<1% of the cases (8). The most frequent combination appears to be found in patients with Ph-negative MPN with concurrent B-cell CLL (8).

We herein report the case of a patient with two hematological malignancies of both lymphoid and myeloid origin.

### Case report

We herein report the case of a 64-year-old man with concomitant diagnosis of high-risk ET and MBL/CLL (Fig. 1).

The patient was referred to the Department of Hematology, Hospital of São Francisco Xavier, West Lisbon Hospital Centre (Lisbon, Portugal) for a consultation due to thrombocytosis of  $700 \times 10^9/l$  detected on routine examination. The patient had a good Eastern Cooperative Oncology Group performance status (score: 1), but had a personal history of diabetes mellitus type 2 and chronic renal disease, and was followed at the Nephrology Department. The patient had no history of previous exposure to myelotoxic drugs or radiation.

During the diagnostic evaluation, in addition to thrombocytosis, the peripheral blood smear revealed the presence of lymphocytosis ( $6.6 \times 10^9/l$ ), with monomorphic small mature lymphocytes and smudge cells. The patient refused bone marrow aspiration and biopsy, so all the tests were performed using peripheral blood.

The clinical presentation was suggestive of ET diagnosis, and both *JAK2V617F* mutation and *BCR/ABL* translocation were tested, the former being positive and the latter negative, which was in agreement with Ph-negative MPN (Fig. 1).

The findings on flow cytometry were consistent with a typical CLL-like phenotype; however, the absolute number of clonal B cells was  $<5 \times 10^9/l$  (25.9% pathological lymphocytes of a total of  $16.1 \times 10^9/l$  leukocytes). Moreover, cytogenetic examination was performed, in order to detect abnormalities characteristic of CLL/SLL (del 11q, del 13q, TP53 gene mutation, del 17p, trisomy 12), and revealed the presence of del 13q (24%), without other rearrangements, and a normal karyotype (Fig. 1).

A whole-body computed tomography scan revealed a massive thrombosis of the left iliac artery. No hepatomegaly, splenomegaly or lymphadenopathy were identified (Fig. 1).

The patient was started on cytoreductive therapy with hydroxyurea 500 mg 3 times/week, achieving an absolute platelet count drop to values within the normal range ( $380 \times 10^9/l$ ).

Concomitantly, the patient was started on hypocoagulation treatment with a vitamin K antagonist (warfarin with a 5 mg/day initial dose, regularly adjusted according to international normalized ratio), for  $\geq 6$  months and until complete resolution of the thrombi.

This patient is currently on surveillance and did not develop other thrombotic events, exhibiting clinical improvement with moderately reduced claudication during the course of treatment.

### Discussion

It remains unclear whether there is a specific mechanism connecting the two events described herein, in terms of whether there is a molecular association between the two, or if

<u>ET</u>	<u>MBL</u>
High PTL count	Clonal B-cells $< 5 \times 10^9/l$
<i>JAK2V617F</i> +	Presence of CLL-like phenotype
<i>BCR/ABL</i> –	del (13q) +
Thrombotic event	No organomegaly
Improvement with HU	No lymphadenopathy
	No other extra-medullary disease
	No therapy need

Figure 1. Patient clinicolaboratorial findings supporting the coexistence of ET and MBL. CLL, chronic lymphocytic leukemia; ET, essential thrombocythemia; HU, hydroxyurea; MBL, monoclonal B-cell lymphocytosis; PTL, platelets; FC, flow cytometry.

they are two independent events developing simultaneously in genetically predisposed individuals.

There is no clear evidence of the pathogenetic association between myeloproliferative and lymphoproliferative diseases. However, given the higher risk of LPN development in MPN patients reported in larger studies, the genomic instability characteristic of MPNs may play a role in the subsequent LPN occurrence (9).

Since both groups of diseases usually have a slowly progressive, indolent course, which may continue for decades, it may be difficult to establish the chronological onset of the occurrence of the two diseases in the same patient.

One hypothesis includes the possibility of the two diseases originating from common progenitors; this hypothesis would be supported by the presence of the *JAK2V617F* mutation in both myeloid cells and B lymphocytes (10).

Another hypothesis is that these are two independent diseases occurring from different progenitors, and having different etiopathogenetic routes. To support this hypothesis, the criteria should include absence of the *JAK2V617F* mutation from the lymphoid cells, as reported previously (11,12).

It is generally accepted that myeloid and lymphoid neoplasms emerge and progress independently. However, there are difficulties when trying to identify a biclonal origin of the two lymphoid and myeloid clones, evidence of which is still lacking (4).

Although an association may be found incidentally, the hypothesis that the two neoplasms may be related requires a close look at the two clones involved.

There is evidence of lymphoproliferative and myeloproliferative events running consistently through the same family. Such evidence includes the occurrence of B-cell malignancies and ET in different generations of the same family (13).

There are already some references in the literature supporting a common progenitor, as in Tabaczewski *et al* (14), which have reported the hypothesis that there may be an initial 'trigger hit' occurring in a pre-*JAK2* common early progenitor multipotential hematopoietic stem cell that can differentiate into both lymphoid and myeloid pathways, and subsequent additional molecular events that could promote myeloid and lymphoid differentiation, leading to the development of two diseases of likely identical origin, but different lineages.

In-depth knowledge of the origin and nature of the concomitance of these two events is currently lacking. To date, there is

no evidence supporting the presence of a common and unique stem cell capable of giving rise to both leukemic and myeloid clones.

The sparse number of cases of simultaneous diagnoses of MPNs and LPNs explains the difficulty in finding consistent explanations that may apply to all cases.

Further studies are required to elucidate the molecular pathogenesis of these underlying events. There remains the question of how to treat efficiently these patients when the two conditions progress simultaneously, and whether there should be different indications regarding the timing of the treatment.

The occasional reports of ET coexisting with MBL/CLL in the same patient do not allow a precise understanding of the origin or proof of whether the two malignancies share a common etiopathogenesis.

In conclusion, it would be interesting to compare genetic biomarkers of the two diseases in both identified clones, in order to report whether they share any common pathways. More studies are required to evaluate the genomic link between these two diseases and to elucidate whether their concomitance is coincidental, or if there is an association between these two entities.

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#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

#### Authors' contributions

FM contributed to the conception and design of the study, drafted and wrote the manuscript, and revised it critically for important intellectual content; PSS and APA contributed to the conception and design of the study, analysis and interpretation of the data, and revised the paper; JMP, RL, SM, JFV and FL analyzed the data and revised the paper. All authors have read and approved the final version of the manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Patient anonymity and consent were guaranteed, in accordance with the Declaration of Helsinki.

#### Competing interests

The authors declare that they have no competing interests.

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