Concomitant Myeloproliferative and Lymphoid Neoplasms in Two Patients Positive for *JAK2* V617F Mutation. Case Report and Literature Review

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Abstract The coexistence of both myeloproliferative and lymphoproliferative neoplasms in the same patient is an uncommon finding. We report two patients who presented such an association. The first patient was initially diagnosed with essential thrombocythemia, developing a clinical and haematological picture consistent with chronic lymphocytic leukaemia several years afterwards. The second patient was diagnosed concomitantly with polycythaemia vera and chronic lymphocytic leukaemia. Both patients were positive for the *JAK2* V617F mutation. In the first patient the chronic lymphocytic leukaemia was asymptomatic, stage A, and did not require any additional treatment, while the second patient presented with generalized large lymphadenopathy (stage B) and chronic lymphocytic leukaemia-related symptoms, requiring chronic lymphocytic leukaemia-directed treatment. It is unclear whether there is a pathogenetic link between the myeloproliferative and lymphoproliferative diseases encountered in these patients, both being probably the result of random mutations occurring in distinct initiating cells. However, given the higher risk of lymphoproliferative neoplasms development in myeloproliferative neoplasms patients reported in larger studies, the genomic instability characteristic to myeloproliferative neoplasms may play a role in subsequent lymphoproliferative neoplasms occurrence.

Keywords Myeloproliferative neoplasm · Chronic lymphocytic leukemia · *JAK2* V617F mutation

Introduction

The myeloproliferative neoplasms (MPN) represent a group of heterogeneous chronic conditions, characterized by the medullar proliferation of at least one myeloid lineage, and increased number of mostly mature elements in peripheral blood [1]. Polycythaemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) represent the three typical MPN negative for the BCR–ABL fusion. A somatic activating point mutation within the Janus kinase 2 (*JAK2*) gene, namely V617F, is the most common molecular marker of the three MPN, being encountered in more than 90 % of PV patients and 40–60 % of the ET and PMF patients [1]. The *JAK2* 46/1 haplotype is a major predisposition factor to the acquisition of the somatic mutation *JAK2* V617F [2].

Chronic lymphocytic leukaemia (CLL), a mature B cell neoplasm, represents one of the most frequent lymphoid neoplasm (LPN), and the most common type of leukaemia in adults, especially in elderly individuals [3].

We report two patients in which both MPN and CLL were diagnosed; the first patient developed CLL several years after the initial diagnosis of ET, while the second patient was diagnosed concomitantly with PV and CLL.

Case Reports

Case 1

A 78-year old female patient was referred in 2005 to the Haematology Department of the “Ion Chiricuță” Cancer

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Institute, Cluj-Napoca, for erythromelalgia crises, lasting for 1 year. During the same period, the patient suffered from two transient ischemic attacks. The physical examination did not reveal any modifications, except the absence of the pulse at the pedious arteries.

The full blood counts revealed an elevated white blood cell count of $14.5 \times 10^9/l$ with a normal differential count except for mild basophilia (neutrophils $8.8 \times 10^9/l$, lymphocytes $3.8 \times 10^9/l$, monocytes $1.5 \times 10^9/l$, basophils $0.2 \times 10^9/l$). The red blood cell count, the haemoglobin and the haematocrit were within normal range; however, the platelets were markedly increased ($1,323 \times 10^9/l$). The bone marrow biopsy revealed bone marrow megakaryocytic hyperplasia, with hyperlobulated megakaryocytes, accompanied by a lymphocytic infiltration of around 25 %. A G-banded bone marrow karyotype was performed, yielding no numeric or structural chromosomal anomalies. Therefore, the diagnosis of ET was established. A regimen of hydroxyurea 1–2 g/day associated with acetyl-salicylic acid (ASA) 75 mg/day was started, the platelets count dropping to values of around $500 \times 10^9/l$. Three years later, in 2008, the analysis of the *JAK2* V617F mutation on DNA obtained from peripheral blood became available in our institution; the patient tested positive for this mutation. The mutant allele burden was estimated at around 10–15 % using a semiquantitative tetra-primer PCR assay [1]. The rs10974944 SNP, tagging the *JAK2* 46/1 haplotype, which predisposes to the acquisition of *JAK2* V617F mutation, was genotyped by a PCR–RFLP (polymerase chain reaction–restriction fragment length polymorphism) assay, as previously described [4]. The patient did not harbour the variant allele (G) of this SNP, neither in heterozygous, nor in homozygous state.

In the three years following the diagnosis of ET, the peripheral lymphocyte count continued to increase constantly, reaching levels of $10\text{--}15 \times 10^9/l$, the patient remaining asymptomatic. In March 2006, a second bone marrow biopsy indicated an important infiltration (around 60 %) by small lymphocytes of mature appearance, positive for CD5, CD19, CD20 and CD23 markers, negative for cyclin D1, along with the megakaryocytic hyperplasia. The immunophenotype of the peripheral lymphocytes, which was determined at a later time by flow cytometry, shown the following profile: CD5 83 %, CD19 68 %, CD20 82 %, CD5 62 %, CD22 83 %, CD23 77 %, consistent with the CLL diagnosis. At the time the patient had no lymphadenopathy or hepatosplenomegaly, no significant anaemia was present and the platelets were within normal range. Therefore a diagnosis of CLL stage A, according to the Binet staging system [5], appearing in a patient with previously diagnosed ET, was established. The patient required no additional treatment for CLL, given the lack of symptoms and the early stage. The latest blood check-up,

performed in May 2011, revealed normal platelet count ($410 \times 10^9/l$), normal haemoglobin (12 g/dl), elevated white blood cell count ($21 \times 10^9/l$, with an absolute lymphocytosis of $15 \times 10^9/l$). The patient was still asymptomatic and without any modifications upon the physical examination. Hydroxyurea was continued, 1 g/day.

Case 2

A 75 year old male patient was referred to the Haematology Department of the “Ion Chiricuță” Cancer Institute, Cluj-Napoca, for a persistent, generalized lymphadenopathy. The patient complained of vertigo and visual troubles, lasting for several years. He also complained of profuse night sweating and weight loss, occurring over the past year. The physical examination revealed the following: plethoric facies, generalized lymphadenopathy (2–3 cm diameter), splenomegaly (5 cm bellow the costal margin) and hepatomegaly (2 cm bellow the costal margin). The patient had dyslalia and a mild motor deficit on the left side, consequences of a stroke from which the patient had been suffered 2 years ago. An ulceration which appeared one year before and measured 3/2.5 cm at the time of the physical examination, has also been observed, in the right malar region. This lesion was most probably an ulcerating basal cell carcinoma.

The full blood counts revealed an increased red blood cell count ($6.7 \times 10^{12}/l$); the haemoglobin was 18 g/dl, while the haematocrit was 58 %. Based on these findings, the diagnosis of PV was suspected. The white blood cell count, which was markedly elevated, had a value of $55 \times 10^9/l$ (neutrophils $13.5 \times 10^9/l$, lymphocytes $38 \times 10^9/l$, monocytes $2.2 \times 10^9/l$, basophils $1.1 \times 10^9/l$). The immunophenotype of the peripheral lymphocytes, which was determined by flow cytometry, shown the following profile: CD5 97 %, CD19 80 %, CD20 80 %, CD22 81 %, CD23 35 %, consistent with a B-cell chronic lymphoproliferative disease, most probably CLL. The *JAK2* V617F mutation analysis on DNA obtained from peripheral blood shown a positive result; the mutant allele burden was estimated at around 25 %. The patient harboured the variant allele (G) of the *JAK2* rs10974944 SNP, in homozygous state.

The bone marrow biopsy revealed a 95 % cellularity, with a massive infiltration by small lymphocytes of mature appearance, positive for CD5, CD19, CD20 and CD23 markers and negative for cyclin D1. A megakaryocytic hyperplasia, with dysplastic, hyperlobulated nuclei was also noted.

A diagnosis of PV with concomitant CLL, stage B (Binet) was made. After four consecutive phlebotomies (300 ml blood/phlebotomy), the haemoglobin level dropped to 15 g/dL, while the haematocrit dropped to 50 %.

The patient continued phlebotomies 1–2 per week, until haematocrit reached the 40–45 % range. Maintenance phlebotomies 1–2 per month are planned for the near future. The patient was also given low dose ASA (75 mg/day), chlorambucil 8 mg/day 5 days/week and methylprednisolone 64 mg/day for two weeks, with subsequent tapering of corticosteroid doses. After about two weeks of treatment, the white cell blood count decreased to $25 \times 10^9/l$ (lymphocytes $8 \times 10^9/l$) and lymphadenopathy was reduced by 80–90 %. Surgical removal of the basal cell carcinoma of the malar region is planned for the near future.

Discussions

The coexistence of MPN and LPN is quite a rare finding. Since both groups of diseases usually have a slowly progressive course, sometimes spanning decades, it is difficult to establish the chronology of the occurrence of the two diseases in the same patient. Several isolated cases of ET in association with CLL have been described [6–12]. Also PV in association with CLL has been described in a few patients [13]. Probably due to the poor prognosis of the PMF, the association between this MPN and CLL is less likely to occur. Vannucchi and colleagues evaluated the risk of developing a lymphoproliferative disorder in a large cohort of 820 MPN patients (353 with PV and 467 with ET) [14]. They noted the development of a LPN in 11 patients, after a median period of latency of 68 months; of these 11 patients, 4 (2 with PV and 2 with ET) developed CLL. They concluded that the risk of developing a CLL was increased both in PV (12.35-fold) and ET (12.49-fold), compared to the general population. All the CLL patients were positive for *JAK2* V617F mutation; interestingly, they found the *JAK2* V617F in tumoral lymphoid cells in one CLL patient.

A similar analysis has been performed very recently by Rumi and colleagues, on a larger series of MPN patients, analyzing 1915 MPN patients [15]. The median follow-up was 5.2 years; 22 MPN patients (1.1 %) developed a LPN in their lifetime. The authors concluded that the risk of developing a LPN in MPN patients was increased 2.79-fold compared to the general population. They were able to analyze *JAK2* V617F status in 16 of the 22 MPN patients who developed a LPN. There were both *JAK2* mutated and wild-type patients, which is in contrast to the report of Vannucchi and colleagues, who found only *JAK2* mutated patients, among those developing a LPN [14].

In such cases of concomitance of MPN and LPN, it is difficult to establish the chronology of the molecular events leading to the two diseases. One scenario supposes that the two diseases originate from common progenitors; this idea

would be supported by the presence of *JAK2* V617F mutation both in myeloid cells and B lymphocytes [12]. Other possible scenario supposes that the two diseases originate from different progenitors; this idea would be supported by the absence of *JAK2* V617F mutation from the lymphoid cells, as observed by some authors [10], [13]. In this latter situation, there would be a milieu of genomic instability, leading to the acquisition of *JAK2* V617F mutation in the myeloid progenitors, and to the acquisition of other mutations in the B lymphocytes progenitors. This milieu of genomic instability is probably different from the *JAK2* V617F-predisposing *JAK2* 46/1 haplotype, as Rumi and colleagues did not find differences between the distribution of this haplotype in patients with both LPN and MPN and patients with MPN only [15].

In conclusion, we described in our report two patients positive for the *JAK2* V617F mutation, who were diagnosed with both MPN and LPN, an uncommon association. Clarification is needed whether the concomitance of the two diseases is pure coincidental, or there is a causative relation between the two groups of diseases.

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References

1. Jones AV, Kreil S, Zoi K et al (2005) Widespread occurrence of the *JAK2* V617F mutation in chronic myeloproliferative disorders. *Blood* 106:2162–2168
2. Trifa AP, Cucuianu A, Petrov L et al (2010) The G allele of the *JAK2* rs10974944 SNP, part of *JAK2* 46/1 haplotype, is strongly associated with *JAK2* V617F-positive myeloproliferative neoplasms. *Ann Hematol* 89(10):979–983
3. Shanafelt TD, Byrd JC, Call TG, Zent CS, Kay NE (2006) Narrative review: initial management of newly diagnosed, early-stage chronic lymphocytic leukemia. *Ann Intern Med* 145:435–447
4. Trifa AP, Cucuianu A, Popp RA (2010) Development of a reliable PCR-RFLP assay for investigation of the *JAK2* rs10974944 SNP, which might predispose to the acquisition of somatic mutation *JAK2* V617F. *Acta Haematol* 123(2):84–87
5. Binet JL, Auquier A, Dighiero G et al (1981) A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 48(1):198–206
6. Gabrail NY, Martin TW (1998) Coexistence of essential thrombocythemia and chronic lymphocytic leukemia. *Acta Haematol* 85:31–33
7. Marcos Sanchez F, Juarez Ucerlay F, Lobato de Blas C, Llanos del Ama ML, Duran Perez-Navarro A (1995) Simultaneous presentation of chronic lymphocytic leukosis and essential thrombocythemia. *Ann Med Intern* 12(11):566
8. Bizzaro N (1998) Chronic lymphocytic leukaemia in a patient with essential thrombocythemia. *Clin Lab Haematol* 20:377–379
9. Robak T, Urbńska-Ryś H, Góra-Tybor J et al (2003) Coexistence of chronic lymphocytic leukemia and essential thrombocythemia. *Leuk Lymphoma* 44:1425–1431
10. Henry L, Carillo S, Jourdan E, Arnaud A, Brun S, Lavabre-Bertrand T (2007) Association of essential thrombocythemia and

- chronic lymphocytic leukemia: absence of the V617F JAK2 mutation in the lymphoid compartment. *Am J Hematol* 82:500–501
11. Tabaczewski P, Nadesan S, Lim SH (2009) Zap-70 positive chronic lymphocytic leukemia co-existing with Jak 2 V617F positive essential thrombocythemia: a common defective stem cell? *Leuk Res* 33(6):854–855
 12. Kodali S, Chen C, Rathnasabapathy C, Wang JC (2009) JAK2 mutation in a patient with CLL with coexistent myeloproliferative neoplasm (MPN). *Leuk Res* 33(12):e236–e239
 13. Hussein K, Brakensiek K, Ballmaier M et al (2006) B-CLL developing in a patient with PV is not affected by V617F mutation of the Janus kinase 2. *Eur J Haematol* 77(6):539–541
 14. Vannucchi AM, Masala G, Antonioli E et al (2009) Increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative myeloproliferative neoplasms. *Cancer Epidemiol Biomarkers Prev* 18(7):2068–2073
 15. Rumi E, Passamonti F, Elena C et al (2011) Increased risk of lymphoid neoplasm in patients with myeloproliferative neoplasm: a study of 1,915 patients. *Haematologica* 96(3):454–458