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Concomitant *JAK2* V617F-positive Polycythemia Vera and B-Cell Chronic Lymphocytic Leukemia in Three Patients Originating from Two Separate Hematopoietic Stem Cells

Sabina Swierczek[1], **Jitka Nausova**[2], **Jaroslav Jelinek**[3], **Enli Liu**[4], **Paul Roda**[5], **Jana Kucerova**[2], **Marie Jarosova**[6], **Helena Urbankova**[6], **Karel Indrak**[6], **Josef T. Prchal**[1,*], and **Vladimir Divoky**[2,6,*]

[1]University of Utah, School of Medicine and VAH, Hematology Division, Salt Lake City, Utah 84132, USA

[2]Department of Biology, Faculty of Medicine and Dentistry, Palacky University, 77515 Olomouc, Czech Republic

[3]Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA 19140

[4]Texas Children's Cancer Center; and Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX 77030, USA

[5]Geisinger Hazleton Cancer Center, Hazleton, PA 18201, USA

[6]Department of Hemato-oncology, Faculty of Medicine Palacky University and University Hospital, 77520 Olomouc, Czech Republic

Abstract

The simultaneous occurrence of polycythemia vera (PV) and chronic lymphocytic leukemia (CLL) is a rare event that offers a possibility to study their common origin. PV originates from self-renewing hematopoietic stem cells (HSC) with both lymphoid and myeloid potential(1–3). It has been reported that CLL also originates from self-renewing HSC with a potential for both lymphoid and myeloid differentiation(4, 5). We report 3 females with concomitant CLL and PV whose X-chromosome inactivation patterns of the neoplastic cells revealed that granulocytes/platelets and B-lymphocytes used different X-chromosome alleles. These data indicate that both PV and CLL have arisen independently and from different HSC.

Keywords

PV; CLL; *JAK2* V617F; clonality

Rare concurrent PV and CLL patients have been reported(6–8). In these patients, the *JAK2* V617F mutation, a marker of PV, was absent in the CLL B-cell lineage. These earlier findings did not rule out a possibility that these two distinct hematological disorders had not arisen from the same primitive HSC that was the subject of somatic mutation(s) leading to two different clonal diseases.

Correspondence: Josef Prchal, Division of Hematology, Department of Medicine, University of Utah School of Medicine Room 5C402 SOM, 30 North 1900 East, Salt Lake City, UT 84132; josef.prchal@hsc.utah.edu or Vladimir Divoky, Department of Biology, Faculty of Medicine, Palacky University, Hnevotinska 3, 77515 Olomouc, Czech Republic; divoky@tunw.upol.cz.

We studied three such subjects: Patient 1, a 79-year-old Caucasian female, had PV diagnosed in 1998 and CLL in 2000. Patient 2, a 67-year-old African American female, was diagnosed with PV in 1997 and with B-CLL in 2001. Patient 3, is a 78-year-old Caucasian female whose PV and CLL were diagnosed over 10 years ago. The PV diagnoses were supported by growth of endogenous erythroid colonies (EECs), a hallmark of PV, and the presence of *JAK2* V617F mutation in granulocytes.

The results are summarized in Table 1. Patient 1 had a *JAK2* V617F allelic burden of 50% in the PV clone (granulocytes and monocytes) but not in T- or B-lymphocytes. We also investigated the *JAK2* V617F-positive cells by genotyping individual EEC colonies; 10 EEC were heterozygous, 1 was homozygous, and 2 were without the *JAK2* V617F mutation, consistent with an earlier finding that the *JAK2* mutation in PV is not the primary disease-initiating event(9–11). Similarly, patients 2 and 3 had the *JAK2* V617F mutation in their granulocytes, but none in CD19-positive B- and CD-3-positive T-cells. PV and CLL lineages of all three patients utilized different active X-chromosomes (see Table 1).

Thus, the hematopoietic neoplasms in these individuals with CLL and PV arose from distinct HSC. Earlier reports did not rule out the possibility that these disorders had not arisen from the same HSC that was the subject of further somatic mutation(s) leading to a clone (pre-*JAK2* V617F clone/pre-leukemic CLL clone) that preceded the subsequent *JAK2* V617F PV mutation. This possibility is now conclusively ruled out by the fact that the PV and CLL clones of these females utilized different active X-chromosomes, i.e. their CLL and PV arose from separate HCS. Nevertheless, it is well possible that the presence of as yet-undefined germ-line mutation(s) may predispose all hematopoietic stem cells to somatic events leading to two different hematological malignancies. Such evidence exists for familial clustering of PV and other myeloproliferative disorders(12), and is also suggested from the increased risk of lymphoproliferative neoplasms in MPN(13, 14).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

The *JAK2* V617F mutation and X chromosome clonality analyses in myeloid and lymphoid lineages. We have analyzed T- and B-lymphocytes, granulocytes, monocytes and platelets from three such female patients for specific CD markers of lineage commitment and clonality, including *JAK2* V617F mutation and X-chromosome transcriptional polymorphisms. Patient 1 was heterozygous for an *MPP1* G/T X-chromosome polymorphism (determined by analysis of genomic leukocyte DNA), and myeloid cells (platelets, granulocytes and EEC) expressed the G allele, while the T allele was exclusive for the CLL B-lymphoid lineage (CD19+ cells). Patient 2 was heterozygous for an *FHL1* A/G X-chromosome exonic polymorphism. Her platelet and granulocyte mRNA (originating from the PV clone; reticulocytes do not express *FHL1*) expressed only the *FHL1* A allele. In contrast, the patient's CD19 mRNA expressed only the *FHL1* G allele. Patient 3 was heterozygous for *FHL1* A/G and *G6PD* C/T X-chromosome exonic polymorphisms. Her platelets and granulocytes were clonal, as their RNA expressed only the *FHL1* G allele and *G6PD* C allele (Table 1). In contrast, her RNA isolated from CD19 CLL B-lymphocytes expressed only the *FHL1* A allele and *G6PD* T allele.

	Granulocytes	Platelets	B-lymphocytes	T-lymphocytes
Patient #1				
JAK2 *V617F* % T allele	50%		ND	ND
Allele detected by transcriptional clonality assay using genotype *MPP1* G/T	G	G	T	G/T
Patient #2				
JAK2 *V617F* % T allele	36%		ND	ND
Allele detected by transcriptional clonality assay using genotype *FHL1* G/A	A	A	G	A/G
Patient #3				
JAK2 *V617F* % T allele	13.2%		ND	ND
Allele detected by transcriptional clonality assay using genotype *FHL1* G/A and *G6PD* C/T	G C	G C	A T	A/G C/T

Abbreviations: ND, not detected; *MPP1* G/T, *FHL1* G/A, *G6PD* C/T, genotypes of studied X-chromosomes polymorphisms.