Tzu Chi Medical Journal 2019; 31(1): 60–62

Case Report

Janus kinase 2 V617F mutation in an unrelated peripheral blood stem cell donor

*Shang-Hsien Yang[a,b], Hsiang-Lin Wan[c], Ming-Hui Gu[d], Tso-Fu Wang[b,e]**

[a]Department of Pediatrics, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [b]Buddhist Tzu Chi Stem Cells Center, Hualien, Taiwan, [c]Department of Hematology and Oncology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan, [d]Department of Laboratory Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [e]Department of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

Received : 02-Dec-2017
Revised : 29-Dec-2017
Accepted : 12-Jan-2018

Abstract

Polycythemia vera (PV) is relatively uncommon in early adulthood, and evidence about the prevalence of the Janus kinase 2 (JAK2) V617F mutation in the general population is limited. Here, we report a previously healthy volunteer peripheral blood stem cell (PBSC) donor who developed symptomatic PV with the JAK2 V617F mutation 2 years after PBSC mobilization and harvest. The characteristic mutation was identified retrospectively in the blood sample of the donor at the confirmation typing stage, which was before granulocyte colony-stimulating factor injection. This report presents a safety issue for both donor and recipient of hematopoietic stem cell transplantation. Clinicians should be aware of this during health workup and postdonation follow-up of unrelated PBSC donors. Any abnormal and/or equivocal laboratory data, especially during the donor workup stage, should not be overlooked.

Keywords: *Granulocyte colony-stimulating factor, Janus kinase 2 V617F mutation, Peripheral blood stem cell harvest, Polycythemia vera, Unrelated donor*

Introduction

Granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) have become the major stem cell source for allogeneic hematopoietic stem cell (HSC) transplantation over the past decade. Although most donors experience the discomfort of varying severity during mobilization and/or leukapheresis, PBSC collection in unrelated donors is generally safe [1,2]. G-CSF injection may cause a dramatic rise in the leukocyte count, along with a modest decrease in the hemoglobin level and platelet count. The blood cell counts return to baseline levels by 1 month after cessation of G-CSF administration [1,2]. No specific association has been found between transient variations in the blood cell counts and hematologic malignancies after G-CSF mobilization [3]. No case of acute myelogenous leukemia or myelodysplasia was reported in a prospective study of 2408 unrelated PBSC donors in the National Marrow Donor Program [1]. Myeloproliferative neoplasms (MPNs) have not been reported in PBSC donors who underwent G-CSF mobilization and stem cell harvest. We report a young woman who underwent PBSC harvest and was diagnosed with Janus kinase 2 (JAK2) V617F mutation polycythemia vera (PV) 2 years after donation.

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_189_17

Case report

A 33-year-old, nonsmoking woman volunteer donor was eligible for PBSC donation after a comprehensive workup for donor health assessment. She had no relevant medical history and did not complain of any clinical symptoms. Laboratory study results showed that no abnormalities except her hemoglobin, hematocrit levels, and platelet count were all in the borderline reference range for females (16 g/dL, 50.2%, and 488,000/μL, respectively). Due to clinical urgency in the recipient, PBSC collection proceeded in 1 month.

The donor underwent a standard PBSC harvest procedure in our institution. In brief, she received daily injections of G-CSF (Filgrastim; Kyowa Hakko Kirin Co., Gunma, Japan) for 5 days. Large volume leukapheresis by a continuous flow cell separator (COBE Spectra; Terumo BCT, CO, USA) through peripheral vascular accesses was performed on the 5th day after injection of the 5th dose of G-CSF. Due

**Address for correspondence:*
Dr. Tso-Fu Wang,
Department of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail: tsofu.wang@gmail.com

How to cite this article: Yang SH, Wan HL, Gu MH, Wang TF. Janus kinase 2 V617F mutation in an unrelated peripheral blood stem cell donor. Tzu Chi Med J 2019;31(1):60-2.

to insufficient product CD34+ cells in the first harvest, another leukapheresis was performed after the 6th dose of G-CSF on the following day. Before the first leukapheresis, moderate leukocytosis (29,390/μL) and mild thrombocytosis (511,000/μL) were identified. The hemoglobin and hematocrit levels were 14.5 g/dL and 46.8%, respectively. The donor tolerated the whole procedure of PBSC harvest well. Her leukocyte count peaked after the 6th dose of G-CSF, and the platelet counts were slightly decreased after leukapheresis. The hemoglobin and hematocrit levels were also decreased but were still relatively high for females [Figure 1]. The preharvest CD34+ cell was 40.96/μL and the final product CD34+ cell yield after two collections was 4.85 × 10^6/kg of the recipient's body weight.

Slowly elevating hemoglobin and hematocrit levels without specific discomfort were noted during serial postdonation follow-ups [Figure 1]. The donor was referred to a hematologist for further evaluation 25 months after harvest. She complained of mild headaches, fatigue, and exertional dyspnea for a few months. Extremely high hemoglobin (20.5 g/dL) and hematocrit (62.4%) levels were found, and PV was diagnosed after the characteristic JAK2 V617F mutation was identified by polymerase chain reaction. She then underwent serial phlebotomy and follow-up for PV. Her blood sample at the stage of HLA confirmation typing was retrospectively examined and was positive for the JAK2 V617F mutation. From the limited information reported by the transplantation center, the recipient had not developed any symptoms of PV, but further detailed laboratory results were not available.

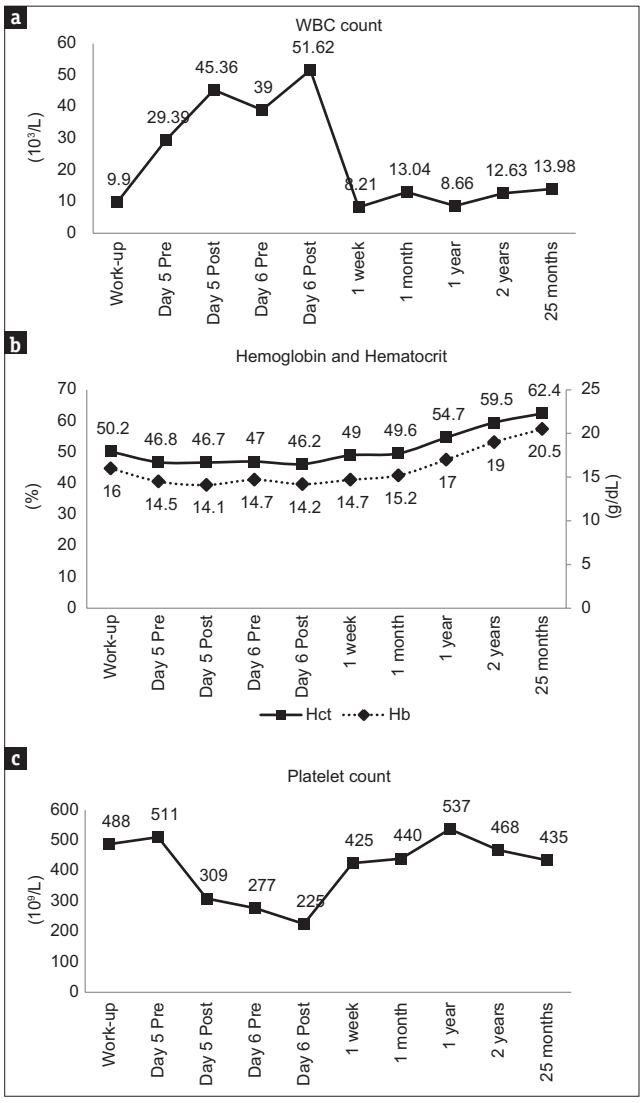

Figure 1: Serial donor blood counts. (a) White blood cell counts. (b) Hemoglobin and hematocrit levels. (c) Platelet counts

Discussion

PV is a clonal hematologic disorder, characterized by unwarranted red blood cell production. Patients have increased risks of thrombosis, myelofibrosis, and secondary acute myeloid leukemia [4]. The JAK2 V617F mutation which results in cytokine-independent growth of hematopoietic cells presents in about 95% patients with PV [5]. To the best of our knowledge, this is the first report of PV diagnosed in an unrelated donor after PBSC donation. The asymptomatic mutation was present before G-CSF administration.

There is limited and controversial evidence about the prevalence of the JAK2 V617F mutation in the general population [6-8]. In a large Demark cohort of 49,488 participants, the JAK2 V617F mutation was detected in 63 individuals, and 48 (76%) of them were eventually diagnosed with MPNs after a median follow-up of 5.4 years [6]. The annual increments of the JAK2 V617F mutation burden and hematocrit were 0.55% and 1.19%, respectively [6]. The allele burden of the JAK2 V617F mutation correlates with the clinical phenotype and disease complications of MPNs [9]. In our donor, the initial asymptomatic, unidentified JAK2 V617F mutation with borderline hemoglobin and hematocrit levels developed into symptomatic PV within 2 years. Although we did not check the quantitative PCR to compare the mutation burden, the incremental hematocrit after G-CSF mobilized PBSC donation was greater (5% per year).

JAK proteins play an important role in the activation of cytokine receptors, which include the G-CSF receptor, through the Janus kinase/signal transducer and activator of transcription signaling pathway after binding with corresponding cytokine ligands [5]. Passamonti *et al*. reported constitutive activation of granulocytes and an increased number of circulating CD34+ cells in MPN patients with the JAK2 V617F mutation [10]. The consequences of exogenous short-term G-CSF activation in persons with the JAK2 V617F mutation remain an interesting question. The leukocyte count and circulating CD34+ cell count of our donor were not extraordinarily high after G-CSF mobilization. Her hemoglobin and hematocrit levels were slightly decreased, whereas the elevated platelet count was an unusual finding compared with that in the literature [1,2].

This case represents a safety consideration for HSC harvest from donors with subclinical JAK2 V617F mutations. Individuals with the characteristic mutation should be permanently deferred from HSC donation, not only because these donors are at risk of evolution to symptomatic MPNs but also because of the possibility of transmission of the mutated JAK2

gene to recipients. Any equivocal laboratory data during donor workup, mobilization/harvest, and postdonation follow-up should not be overlooked. JAK2 V617F mutation should be carefully clarified in all donors with high hemoglobin and/or hematocrit levels. Further investigation is needed to determine whether PBSC mobilization by G-CSF injection accelerates the natural course of PV.

Declaration of patient consent

The authors certify that the patient obtained an appropriate patient consent form. In the form, the patient gave her consent for her clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, King RJ, Rizzo JD, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: Results of a prospective trial from the National Marrow Donor Program. Blood 2009;113:3604-11.
2. Hölig K, Kramer M, Kroschinsky F, Bornhäuser M, Mengling T, Schmidt AH, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. Blood 2009;114:3757-63.
3. Pulsipher MA, Chitphakdithai P, Logan BR, Navarro WH, Levine JE, Miller JP, et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs. BM donation. Blood 2014;123:3655-63.
4. Stein BL, Oh ST, Berenzon D, Hobbs GS, Kremyanskaya M, Rampal RK, et al. Polycythemia vera: An appraisal of the biology and management 10 years after the discovery of JAK2 V617F. J Clin Oncol 2015;33:3953-60.
5. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nat Rev Cancer 2007;7:673-83.
6. Nielsen C, Bojesen SE, Nordestgaard BG, Kofoed KF, Birgens HS. JAK2V617F somatic mutation in the general population: Myeloproliferative neoplasm development and progression rate. Haematologica 2014;99:1448-55.
7. Xu X, Zhang Q, Luo J, Xing S, Li Q, Krantz SB, et al. JAK2(V617F): Prevalence in a large chinese hospital population. Blood 2007;109:339-42.
8. Sidon P, El Housni H, Dessars B, Heimann P. The JAK2V617F mutation is detectable at very low level in peripheral blood of healthy donors. Leukemia 2006;20:1622.
9. Passamonti F, Rumi E. Clinical relevance of JAK2 (V617F) mutant allele burden. Haematologica 2009;94:7-10.
10. Passamonti F, Rumi E, Pietra D, Della Porta MG, Boveri E, Pascutto C, et al. Relation between JAK2 (V617F) mutation status, granulocyte activation, and constitutive mobilization of CD34+ cells into peripheral blood in myeloproliferative disorders. Blood 2006;107:3676-82.