Unstable angina in a peripheral blood stem and progenitor cell donor given granulocyte–colony-stimulating factor

In recent years, clinical trials of allogeneic transplants using growth factor-mobilized peripheral blood stem and progenitor cells (PBPCs) demonstrated rapid hematologic recovery with rates of acute graft-versus-host disease comparable to those with bone marrow transplantation. For normal donors, the collection of PBPCs by apheresis is a feasible alternative to undergoing marrow harvest with anesthesia, and it avoids the potential morbidity associated with marrow collection. However, the administration of growth factors such as granulocyte–colony-stimulating factor (G–CSF) to mobilize PBPCs and the use of apheresis to collect PBPCs are associated with certain well-documented potential side effects. Normal donors given G–CSF may experience bone pain, headache, fatigue, and nausea, all of which are reversible side effects rarely requiring discontinuation of the drug. Because only a relatively small number of normal donors have received G–CSF so far, and because follow-up is limited, the early and long-term safety profile of this drug in normal donors remains incomplete. Indeed, two case reports of potentially serious or even life-threatening adverse events that occurred in normal donors (splenic rupture after a 6-day course of G–CSF at 10 µg/kg/day and anaphylactoid reaction after one dose of G–CSF at 10 µg/kg/day) point out the need for continued close monitoring and notification of such adverse outcomes.[1,2]

We describe a previously healthy donor who developed cardiac ischemia during PBPC mobilization with G–CSF, prior to apheresis. A 46-year-old man agreed to donate G–CSF-mobilized PBPCs to his HLA-matched sister, who was undergoing allogeneic transplant for treatment of multiple myeloma. Both the donor and the recipient consented to participate in a protocol approved by the Human Studies Committee (Washington University School of Medicine, St. Louis, MO) . Evaluation and screening for blood component donation were performed by using a modification of the criteria established by the American Association of Blood Banks.[3] The donor initially denied any preceding cardiac symptoms. Risk factors for coronary artery disease (CAD) included smoking and family history of CAD, with the donor's father having died of a myocardial infarction at the age of 44 years. An electrocardiogram (EKG) performed at initial screening 3 weeks before the first dose of G–CSF was normal.

The donor received G–CSF at 10 µg per kg (910 µg) by subcutaneous injection 4 days before the planned PBPC collection (Day 1). Six hours after the second dose of G–CSF (Day 2), the donor developed palpitations and chest discomfort with minimal exertion. He sought medical attention the next morning (Day 3), complaining of persistent symptoms. At that time, physical examination was unremarkable. However, an EKG revealed trigeminy and new small Q-waves in leads III and AVF and T-wave inversion in leads I, III, and AVF. The third dose of G–CSF was withheld, and the donor was admitted to the hospital for further evaluation and observation.

Troponin levels obtained upon admission and 12 hours later were within normal limits (<0.4 ng/mL). Table 1 provides the complete blood counts; the prothrombin and partial thromboplastin times were within normal limits. A repeat EKG was performed 7 hours later, by which time the symptoms had resolved; EKG revealed no ectopy, but persistent Q- and T-wave changes were shown. On Day 4, the third dose of G–CSF was given, and, after 3 hours of close observation without further symptoms of ischemia, the donor was discharged from the hospital. Three hours after discharge, the donor developed recurrent palpitations and chest discomfort and was readmitted to the hospital. The EKG was unchanged, and repeat troponin levels obtained at the time of readmission were again normal (<0.4 ng/mL).

G–CSF was discontinued, and the planned PBPC collection was canceled, because of concern that the hemodynamic stress of the apheresis procedure may exacerbate the donor's cardiac ischemia. On Day 6, the donor underwent cardiac catheterization, which revealed significant CAD, including 100-percent occlusion of the right coronary artery and of a septal and diagonal branch of the left coronary artery and 50-percent occlusion of the left anterior descending artery. On Day 9, a percutaneous transluminal coronary angioplasty was performed, and a stent was placed in the right coronary artery. The recipient, who had received high-dose cyclophosphamide, was not given the scheduled total body irradiation and was aggressively supported through the following period of neutropenia; she recovered. After a negative cardiac stress test 2 months later, the same donor safely underwent a bone marrow harvest under general anesthesia, and the recipient underwent allogeneic transplant after a second conditioning regimen.

The pathophysiology of unstable angina usually results from the fissuring of atherosclerotic plaque, with development of superimposed platelet- or fibrin-rich thrombin and consequent cardiac ischemia. Several reports have provided supportive evidence that G–CSF can influence platelet aggregation. Several reports identified G–CSF receptors on platelet membranes and demonstrated increased ADP-induced platelet aggregation with G–CSF in vitro[4] and in normal volunteers.[5,6] Using platelets obtained from healthy donors, Avenarius et al.[7] also observed increased collagen-induced platelet aggregation when in vitro tests were per-

TABLE 1. Peripheral blood counts

	Day 1	Day 2	Day 3	Day 4	Day 5
White cells (× 10^9/L)	6.9	27.1	35.6	28.5	39.5
Hemoglobin (dL)	14.3	12.5	14.8	13.6	13.2
Platelets (× 10^9/L)	258	246	270	242	245

formed in the presence of G–CSF and controls. The results of these studies suggest that G–CSF can influence platelet aggregation. The PBPC donor in this report had risk factors for CAD and later admitted to mild exertional chest discomfort 2 weeks before the first dose of G–CSF. Within 6 hours of the second and third doses of G–CSF, the donor developed symptoms and signs of cardiac ischemia, and the subsequent evaluation confirmed significant CAD. The role, if any, of G–CSF in the development of this donor's cardiac ischemia is unclear. Obviously, the donor had preexisting CAD and therefore was at risk for spontaneously developing ischemic symptoms during PBPC mobilization with G–CSF. However, the temporal association of the onset of cardiac ischemia within 6 hours of each of two doses of G–CSF suggests a potential relationship between the administration of G–CSF and the onset of ischemia, perhaps as a result of the increased platelet aggregation observed with G–CSF in some studies.[4-7] Fukumoto et al.[8] previously reported a patient with acute myeloid leukemia who developed angina pectoris before autologous PBPC transplantation while undergoing a conditioning regimen and subcutaneous injection of G–CSF at a dose of 20 µg per kg per day. They argued that G–CSF may predispose a person to thrombosis as a result of leukocytosis and/or granulocyte activation with adherence to endothelium and endothelial injury.[8] In our experience, the association of angina with G-CSF administration is uncommon, with an incidence at our institution of 1 in 162 healthy donors who received G–CSF for PBPC mobilization since 1994. Taken together, this case report and the laboratory evidence of increased platelet aggregation with G–CSF suggest that PBPC donors with a history of atherosclerotic disease or symptoms suggestive of its presence either should not receive G–CSF or, if it is given, should be closely monitored.

Ravi Vij, MD
Douglas R. Adkins, MD
Randy A. Brown, MD
Hanna Khoury, MD
John F. DiPersio, MD, PhD
Division of Bone Marrow Transplantation and Stem Cell Biology
Department of Internal Medicine
Tim Goodnough, MD
Division of Laboratory Medicine
Department of Pathology
Washington University School of Medicine
St. Louis, MO

REFERENCES

1. Becker PS, Wagle M, Matous S, et al. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. Biol Blood Marrow Transplant 1997;3:45-9.
2. Adkins D. Anaphylactoid reaction in a normal donor given granulocyte colony-stimulating factor (letter). J Clin Oncol 1998;16:812.
3. Menitove JE, ed. Standards for blood banks and transfusion services. 18th ed. Bethesda: American Association of Blood Banks, 1997.
4. Shimoda K, Okarmura S, Harada N, et al. Identification of a functional receptor for granulocyte colony-stimulating factor on platelets. J Clin Invest 1993;91:1310-3.
5. Shimoda K, Okarmura S, Inaba S, et al. Granulocyte colony-stimulating factor and platelet aggregation (letter). Lancet 1993;341:633.
6. Kuroiwa M, Okamura T, Kanaji T, et al. Effects of granulocyte colony-stimulating factor on the hemostatic system in healthy volunteers. Int J Hematol 1996;63:311-6.
7. Avenarius HJ, Freund M, Deinhardt J, et al. Effect of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on circulating platelets. Ann Hematol 1992;65:6-9.
8. Fukumoto Y, Miyamoto T, Okamura T, et al. Angina pectoris occurring during granulocyte colony-stimulating factor-combined preparatory regimen for autologous peripheral blood stem cell transplantation in a patient with acute myelogenous leukaemia. Br J Haematol 1997;97:666-8.

Acquired B antigen in a volunteer blood donor

An apparently healthy 66-year-old woman donated blood on September 11, 1995. Her red cells were typed as group A, Rh-positive by the use of monoclonal reagents (Ortho Diagnostic Systems, Raritan, NJ) that do not contain the ES4 clone in the anti-B reagent. The results of routine confirmatory testing by a transfusion service, using monoclonal reagents containing the ES4 clone (Immucor, Norcross, GA) were group AB for the red cell typing, but group A for the plasma typing. The presence of an acquired B antigen was suspected.

Twenty-one previous blood donations of this woman had been typed as group A, Rh-positive, and they had been labeled and distributed for transfusion. Testing of samples from this donation at a reference laboratory confirmed an acquired B antigen. The donor's red cells reacted strongly (4+) with monoclonal anti-B reagents (Gamma Biologicals, Houston, TX; Organon Teknika Corp., Durham, NC; and Immucor), all containing the ES4 clone. Her red cells also reacted strongly (4+) with polyclonal anti-B (Organon). Her red cells were nonreactive with monoclonal anti-B (Ortho), which lacks the ES4 clone. The blood center's medical director referred the donor to her physician because of the association of acquired B antigen with gastrointestinal disease, including carcinoma of the colon and other malignancies.[1] Physical exam revealed a left-sided abdominal mass.