



Splenic rupture secondary to pegfilgrastim in a healthy allogeneic peripheral blood hematopoietic stem cell donor

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Abstract

Granulocyte-colony stimulating factor (G-CSF) is widely used to mobilize peripheral blood stem cells (PBSCs) for hematopoietic cell transplantation (HCT). G-CSF is generally well-tolerated but can cause life-threatening complications such as splenic rupture in rare cases. Long-acting pegfilgrastim (Peg-G) is increasingly used for PBSC mobilization, but its risk for splenic rupture is less well characterized. Here, we report a case of splenic rupture secondary to Peg-G administered for PBSC mobilization in a healthy 25-year-old male haploidentical donor. He presented with left upper quadrant abdominal pain shortly after PBSC harvest 5 days following administration of Peg-G. Computed tomography (CT) revealed splenomegaly with rupture, and small bloody peri-splenic and pelvic ascites. He was managed conservatively, but the next evening his symptoms temporarily worsened, prompting a repeat CT scan, which showed no change. Thereafter, the pain did not recur, and the patient was discharged on day 8. One month later, a follow-up CT demonstrated complete resolution. To our knowledge, this is the first case of splenic rupture secondary to Peg-G for PBSC mobilization in a healthy allogeneic donor and highlights the importance of vigilance for this rare complication when G-CSF or Peg-G is used for mobilization.

Keywords Peripheral blood hematopoietic stem cells · Mobilization · Pegfilgrastim · Splenic rupture

Introduction

Granulocyte-colony stimulating factor (G-CSF) promotes the growth, proliferation, differentiation and maturation of neutrophil precursors. It is widely used to accelerate neutrophil recovery following hematopoietic cell transplantation (HCT) and chemotherapy for both solid tumors and hematological malignancies. G-CSF is also used to mobilize

peripheral blood stem cells (PBSCs) from autologous and allogeneic HCT donors. Pegfilgrastim (Peg-G) is a pegylated form of G-CSF with a prolonged half-life. Administration of single-dose Peg-G in healthy donors has shown no significant difference in efficacy or safety compared with daily G-CSF [1]. Accordingly, in Japan, a single dose of 7.2 mg Peg-G was approved for related donor and unrelated donor PBSC mobilization in 2022 and 2024, respectively.

The use of allogeneic PBSC grafts over other sources, including bone marrow has steadily increased in the Asia-Pacific region for both related and unrelated allogeneic HCT. This is likely due to improved logistical feasibility and the reduced physical burden on donors due to general anesthesia not being required for PBSC collection [2].

Daily G-CSF and single-dose Peg-G are both generally safe and well-tolerated, but rare life-threatening complications can occur, including splenic rupture.

We herein report the first case of splenic rupture secondary to Peg-G in a healthy allogeneic PBSC donor.

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Case presentation

A 25-year-old healthy male agreed to serve as a haploidentical HCT donor for his father with *BCR-ABL1* positive acute lymphoblastic leukemia. The donor's height, weight, and body surface area were 163.6 cm, 70.2 kg, and 1.76 m², respectively. The donor's past medical history, physical examination, routine blood tests, chest X-ray, and electrocardiogram were all unremarkable.

A single 7.2 mg dose of Peg-G was administered in the outpatient setting to mobilize PBSC. The donor subsequently reported bone pain and fatigue that responded well to acetaminophen. On day 4, he underwent planned admission to facilitate PBSC collection. His white blood cell (WBC) count was $68.6 \times 10^3/\mu\text{L}$ with a CD34 positive (CD34+) cell count of $142/\mu\text{L}$ that day. On day 5, his WBC count was $68.3 \times 10^3/\mu\text{L}$ with a CD34+ cell count of $132/\mu\text{L}$, indicating effective mobilization. Therefore, apheresis was initiated that morning. Blood was drawn from the right basilic vein and returned via the left cephalic vein. The total processed blood volume was 7,607 mL, and the maximum flow rate was 65.2 mL/min. A total of 659 ml of ACD solution was used as an anticoagulant. During the procedure, systolic blood pressure remained around 130–140 mmHg, and no remarkable adverse events were observed. We successfully harvested 8.1×10^6 CD34+ cells/kg of the recipient body weight.

Approximately 1 h after completion of apheresis, he suddenly developed left upper quadrant abdominal pain. His vital signs at that time were stable, with a blood pressure of 112/67 mmHg, pulse rate of 78/min, and body temperature of 37.0 °C. Abdominal computed tomography (CT) demonstrated splenomegaly and a small amount of bloody ascites, with a CT attenuation value of approximately 50 Hounsfield units, near the spleen and in the pelvic cavity (Fig. 1). These findings were consistent with splenic rupture. Because there was no extravasation of contrast, conservative management with careful observation was chosen. By the following morning, his abdominal pain, bone pain, and fatigue had improved, with only mild abdominal tenderness remaining. His WBC count declined appropriately, and his hemoglobin and hematocrit remained stable, all reassuring that his internal bleeding had resolved. However, later in the evening on day 6, his abdominal pain worsened. Fortunately, a repeat CT showed stable findings. Thereafter, the pain did not recur, and he was discharged on day 8.

Upon routine follow-up 1 month later, CT showed improved splenomegaly and complete resolution of bloody ascites (Fig. 2).

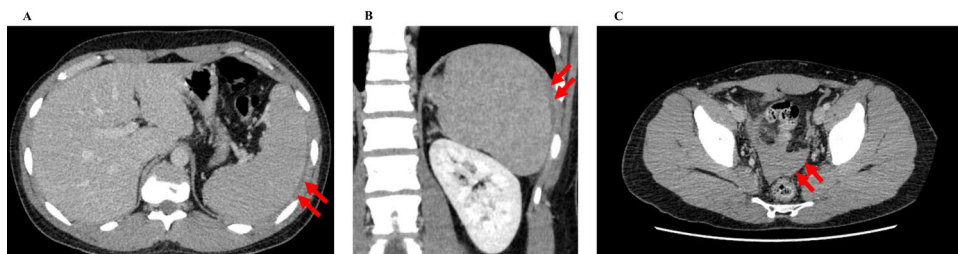
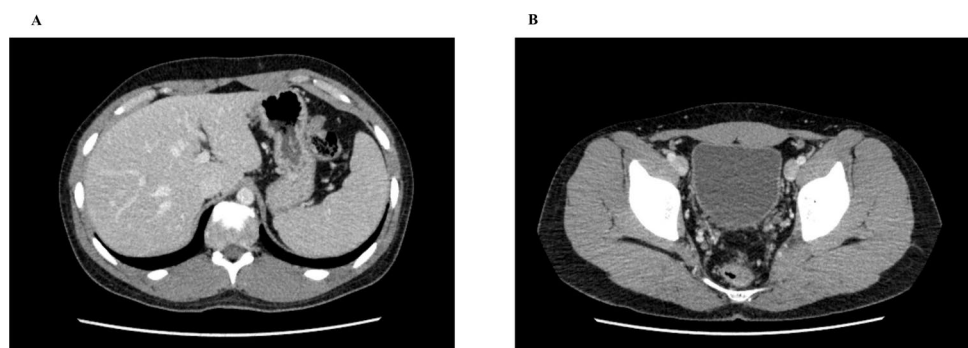


Fig. 1 Computed tomography (CT) scans at the onset of splenic rupture. **A** Coronal CT image of the abdomen. **B** Sagittal CT image of the abdomen. **C** Coronal CT image of the pelvis. The double arrows

indicate splenomegaly and small peri-splenic and pelvic bloody ascites, with a CT attenuation value of approximately 50 Hounsfield units

Fig. 2 Follow-up CT scans obtained approximately one month later. **A** Coronal CT image of the abdomen. **B** Sagittal CT image of the abdomen. The spleen size was reduced, with complete resolution of the bloody ascites



Discussion

G-CSF is generally considered safe and well-tolerated for mobilization. Common side effects include bone pain, fatigue, headache, insomnia, loss of appetite, and nausea [3]. Life-threatening complications are extremely rare. However, cases of myocardial infarction, cerebrovascular disorders, and splenic rupture have been reported [4, 5].

To date, eight cases of splenic rupture associated with G-CSF used to mobilize PBSC in healthy donors have been reported, all of which involved daily G-CSF administration (Table 1) [6–13]. Although four cases of splenic rupture associated with Peg-G have been reported, Peg-G in those cases was used for neutrophil recovery following chemotherapy or to mobilize PBSC from autologous HCT recipients [14–17]. To our knowledge, the case presented here is the first report of splenic rupture due to Peg-G in a healthy allogeneic PBSC donor.

The mechanism of G-CSF associated splenic rupture is thought to involve parenchymal congestion secondary to the massive extramedullary hematopoiesis and intrasplenic sequestration of peripheral blood cells [18]. It has also been suggested that rapid changes in splenic volume, rather than the absolute splenic size, may play a more important role in the development of splenic rupture [14]. In healthy volunteers receiving Peg-G, the mean WBC count reportedly peaks on day 4 at $49.5 \times 10^9/\text{L}$, with maximum observed value of $68.5 \times 10^9/\text{L}$ [1]. In clinical practice, the WBC count of a similar or even higher magnitude is sometimes encountered. While daily G-CSF allows for dose adjustment or discontinuation based on the WBC count, Peg-G does not permit dose modification once administered. Consequently, Peg-G may be less amenable to controlling rapid hematopoietic expansion and

spleen enlargement than daily G-CSF and may therefore be associated with a greater risk of splenic rupture. However, this will require further study to verify.

It is not known what donor characteristics are associated with splenic rupture following G-CSF. In the eight previously reported published cases of splenic rupture associated with daily G-CSF administration, donors tended to be younger (22–51 years, median 34 years) and predominantly male (five male and three female) (Table 1) [6–13]. In addition, most events occurred on day 5 to 6 of mobilization, coinciding with the period of maximal splenic enlargement [19]. In our case, symptoms also developed on day 5 in a 25-year-old male. Its possible such donors may be more reactive to G-CSF; therefore, providers should remain vigilant for splenic rupture at times when splenic enlargement peaks following Peg-G in similar donors.

In our case, symptoms developed approximately 1 h after completion of apheresis. Although a potential contribution of the apheresis procedure itself cannot be excluded, the procedure was relatively short in this case, lasting just 2 h and 16 min and processing less than two circulating blood volumes due to good mobilization. The donor tolerated apheresis well with no major hemodynamic alterations. In addition, 659 ml of ACD solution was used as an anticoagulant, which is not considered excessive at our institution. Previous reports have not described the involvement of ACD solution in splenic rupture [6–13], and the half-life of ACD is shorter than that of heparin [20]. Therefore, we believe it unlikely that ACD or hemodynamic shifts associated with apheresis contributed to the splenic rupture or prompted any subsequent bleeding.

Interestingly, non-traumatic splenic rupture, as observed in our case, has also been reported in settings other than G-CSF administration, including infections, hematological and non-hematological neoplasms, as well as medical

Table 1 Summary of reported cases of splenic rupture secondary to daily granulocyte-colony stimulating factors (G-CSF) induced peripheral blood stem cell (PBSC) mobilization in healthy donors

Authors	Age/Sex of recipient	Relation to recipient	G-CSF dose	Days of splenic rupture	Treatment
Daniel JA et al. 2024 [6]	29/M	Not described	Not described	Not described, after discharge	Interventional radiology
Akyol G et al. 2014 [7]	40/F	Related	11 µg/kg/day	Day 4, 2 h after administration of G-CSF in the evening	Conservative measures
Nuamah NM et al. 2006 [8]	34/F	Related	20 µg/kg/day	Day 6, during apheresis	Splenectomy
Dincer AP et al. 2004 [9]	43/M	Related	20 µg/kg/day	Day 5, during apheresis	Conservative measures
Balaguer H et al. 2004 [10]	51/M	Related	10 µg/kg/day	Day 6, 12 h after the second apheresis	Splenectomy
Kröger N et al. 2002 [11]	Not described/M	Not described	10 µg/kg/day	Day 5	Conservative measures
Falzett F et al. 1999 [12]	33/F	Related	16 µg/kg/day	Day 6, after the third apheresis	Splenectomy
Becker PS et al. 1997 [13]	22/M	Related	10 µg/kg/day	Day 10	Splenectomy

procedures such as colonoscopy [21]. A systematic review summarized 613 cases of splenic rupture occurring in patients without trauma, risk factors, or previously diagnosed disease. According to this review, 10 cases were associated with G-CSF administration. Therefore, clinicians should be aware that splenic rupture can rarely occur during G-CSF administration.

Peg-G is effective for PBSC mobilization, requires just a single dose, and can improve efficacy of PBSC collection thereby decreasing resources used for each collection. As with all medicines, Peg-G can also cause adverse effects including splenic rupture. Fortunately, the splenic rupture our donor suffered resolved without invasive intervention. However, in the eight previous reported cases (Table 1), four required splenectomy and one required interventional radiology. When Peg-G is used, as with daily G-CSF, clinicians should remain vigilant for this potentially life-threatening complication and promptly evaluate donors who develop sudden abdominal pain. Donors should be informed of this risk, advised to avoid strenuous physical activity, and instructed to report any abdominal symptoms immediately. Ensuring donor safety must remain paramount.

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Data availability The data that support the findings of this study are available on request from the corresponding author: toubai@med.id.yamagata-u.ac.jp. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflicts of interest Ryo Takahashi, Kouichi Oya, Yuki Ishizawa, Yusukey Nagano, Ryo Sato, Masashi Hosokawa, Akane Yamada, Takuma Suzuki, Keiko Aizawa, and Daniel Peltier declare no conflicts of interest. Satoshi Ito has received research funding from Chugai. Hisayuki Yokoyama has received honoraria from Kyowa Kirin and Chugai and is an editor of the International Journal of Hematology. Tomomi Toubai has received research funding from Chugai.

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