Spontaneous splenic rupture in a healthy allogeneic donor of peripheral-blood stem cell following the administration of granulocyte colony-stimulating factor (g-csf). A case report and review of the literature

Human granulocyte colony-stimulating factor (G-CSF) is a hematopoietic hormone promoting the growth, proliferation, differentiation and maturation of myeloid and leukocytic lineages. G-CSFs have been used to improve granulocyte count in neutropenic patients, reduce the incidence and duration of neutropenia in patients receiving cytotoxic chemotherapy and to mobilize peripheral blood stem cells prior to leukapheresis for using in both autologous and allogeneic hematopoietic cell transplantation. In general, side-effects are mild to moderate and life threatening side-effects like splenic rupture are very rare. We herein, report a case of spontaneous splenic rupture secondary to high-dose G-CSF use (20 μg/kg/day), in a healthy female allogeneic donor of peripheral-blood stem cell (PBSC).

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Neutropenia is a serious sequela in patients taking cytotoxic chemotherapy for various malignancies, HIV infected patients on antiviral therapy and those with myelodysplasia. G-CSF is used to correct neutropenic state by promoting the growth, proliferation, differentiation and maturation of neutrophil precursors. In addition to recruiting more leukocytes, G-CSF promotes the functional capacity of peripheral white blood cells. It is also frequently used to mobilize peripheral blood stem cells (PBSC) prior to both autologous and allogeneic bone marrow transplantation.[1,2] Long-term use of these agents can result in splenomegaly and extramedullary hematopoiesis. Side-effects are generally mild to moderate including bone and joint pain, headache, fever, rhinitis, rashes, fatigue, thrombocytopenia and injection site reactions.[2] Life-threatening complications such as stroke, myocardial infarction and splenic rupture, resulting from short-term or long-term use of these agents, however rare, can occur. We here-in, report of a case of spontaneous rupture of the spleen secondary to G-CSF (filgrastim) therapy in an otherwise healthy allogeneic donor of peripheral blood stem cells.

Case report

A 34-year old male patient diagnosed with chronic myeloid leukemia (CML) and tested positive for BCR-ABL fusion protein, was given imatinib mesylate (glivec) therapy for one year. Follow-up bone marrow aspiration revealed an increase in myeloid:erythroid ratio, lymphocytes and megakaryocytes and 5% blasts. He was scheduled for allogeneic stem cell transplantation from his 34 years old sister, after informed consents were received from both the donor and recipient.

The donor, an otherwise healthy individual, with a body weight of 60 kg and a height of 170 cm, had no remarkable previous medical history except a 10-year history of smoking (5-10 cigarettes daily). Her physical examination, chest x-ray, electrocardiogram, complete blood count, blood chemistry were normal. Serologic tests for Hepatitis B and C, Epstein-Barr virus, Herpes virus 1 and 2, Cytomegalovirus, HIV and Toxoplasma were all negative. Anti-hepatitis A IgG was positive, but negative for IgM.

Figure 1. CT scan showing perihepatic and perisplenic fluid with density of 50HU signifying hemoperitonuem.

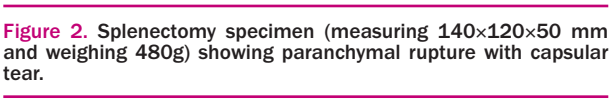

Figure 2. Splenectomy specimen (measuring 140×120×50 mm and weighing 480g) showing paranchymal rupture with capsular tear.

The donor was started on daily G-CSF (filgrastim) therapy, at a dose of 20 μg/kg/day (10 μg/kg twice daily) for 5 days. Leukopheresis was started on the morning of day 6 (white blood cell count (WBC) of 50×10^9/L) after receiving an additional dose of filgrastim (10 μg/kg). Three hours after the start of the apheresis procedure, she developed a severe sharp left upper quadrant pain. The procedure was immediately halted and her immediate vital signs showed a blood pressure of 100/67 mmHg, a pulse rate of 87/min and a body temperature was 36.7°C. On physical examination, she had left upper quadrant tenderness with rigidity and a palpable spleen. An immediate complete blood count revealed hemoglobin of 10.1g/dl, hematocrit of 29.8% and platelet count of 237 $\times10^9$/L. A bedside abdominal ultrasound disclosed splenomegaly with no intraabdominal fluid. Three hours later, she developed tachycardia with mild hypotension (pulse rate of 107/min and blood pressure of 94/52 mmHg) and her pain began radiating to her left shoulder. Her hematocrit and hemoglobin levels fell to 22.6% and 7.8, respectively. An abdominal computed tomography (CT) scan with intravenous contrast subsequently showed widespread intraabdominal fluid (density of 50HU signifying hemoperitoneum), and a cortical segment disruption at the middle section of the posterior

Table 1. Summary of Characteristics of Some Previously Reported Cases of Splenic Rupture following G-CSF administration for Hematopoietic Progenitor Cell Mobilization.

Authors (Reference number)	Age/Sex of recipient	Medical condition of recipient	G-CSF dose	Day of Splenic Rupture	Treatment	Splenic size(mm) and weight
Falzetti F. et al. (ref.no 7)	33/M	Healthy donor	16 μg/kg/day	Day 6 after 2nd apheresis	Splenectomy	150x100x65 445g
Dincer AP et al (ref. no 11)	43/M	Healthy donor	20 μg/kg/day	During apheresis after 5-day G-CSF use	Conservative measures	Normal size (dimensions not given)
Balaguer H. et al. (ref. no 10)	51/F	Healthy donor	10 μg/kg/day	Day 6, 12hrs after 3rd apheresis	Splenectomy	113x191x161, (weight not given)
Kasper C. et al (ref. no 6)	22/M	Acute Myeloid Leukemia under chemotherapy and G-CSF priming	5 μg/kg/day	Day 10	Splenectomy	115x70x50, 186 g
O`Malley DP et al (ref. no 9)	60/M	Neutropenia associated with Myelodysplastic Syndrome	5 μg/kg/day	72hrs after 3-day consecutive treatment	Mortality	Size not reported, 225g
Pitini V et al. (ref. no 8)	38/F	Breast cancer under chemotherapy and G-CSF priming	5 μg/kg/day	Day 13, 24hr after 1st apheresis	Splenectomy	150x120x65, 480g

part of the spleen, suspicious of splenic rupture (Figure 1). A diagnosis of splenic rupture was made and patient underwent a successful emergent splenectomy.

The spleen removed was moderately enlarged measuring 140×120×50 mm and weighed 480 g (normal adult spleen measures 120×70×25 mm and weighs 200g). Macroscopic examination revealed a 40×10 mm length of subcapsular and paranchymal rupture and a 5×30 mm area of capsular tear due to intraoperative maneuver (Figure 2). Histology showed congestive changes in the parenchyma with massive extramedullary myelopoiesis and scarce megakaryocytes. Her postoperative course was uneventful and was discharged on 5th postoperative day. Her brother, after a successful transplantation, is currently doing well clinically with a negative bcr/abl test and is on remission with 100% full-donor chimerism.

Discussion

G-CSFs are generally regarded to be safe and mostly well tolerated. Clinical adverse effects are generally mild or moderate (2,3). Life-threatening complications such as spontaneous splenic rupture, are extremely rare. There are few reports on spontaneous splenic rupture occurring in both healthy donors of PBSC and patients undergoing PBSC mobilization in the international literature, most of which were successfully managed with splenectomy.[4-11] Summary of some previously reported cases is presented in Table 1. Two of these cases resulted in fatality; one in a patient with acute monocytic leukemia[4] and the other, in a patient with myelodysplastic syndrome.[9]

In the case presented above the donor experienced a severe and sharp left upper quadrant pain radiating to her left shoulder (Kehr`s sign) three hours into the leukapheresis procedure. There was no incident of trauma prior to or during the procedure. Splenic rupture occurring during G-CSF use is generally thought to be due to the paranchymal congestion secondary to the massive extramedullary myelopoiesis and intrasplenic sequestration of peripheral blood cells, as observed in this case. However, occurrence of the splenic rupture during apheresis is worth noting as there might be possibly some factors of the procedure influencing splenic rupture, such as excessive saline infusion, blood flow rate, volume of blood processed e.t.c. Further studies are needed to evaluate the potential role of apheresis in spontaneous splenic rupture occurring in allogeneic donors.

The donor in our case was given 10 μg/kg/12h of G-CSF for 5 days and an additional dose the morning of apheresis, aimed at increasing yield. In reported cases of splenic rupture in healthy donors under G-CSF treatment, doses ranging between 5-20 μg/kg/day were used. Studies conducted on healthy individuals comparing high-dose to standard-dose of G-CSF use showed that high-dose results in significantly higher number of progenitor cells (CD34+ cells) and reduced number of apheresis required to obtain enough numbers of CD34+ cells (generally 2,5-5.0×10^6/kg) for allogeneic PBSC transplant.[12,13] Similar results have been reported on trials conducted on patients using high-dose G-CSF.[14,15] However, the marked increase in PBSC mobilization observed with high doses is expected to be associated with more intense extramedullary hematopoiesis and splenic congestion, hence a marked increase in risk of splenic rupture. Although the splenic rupture in our case cannot be said to have been cause by the high-dose G-CSF used, it is our believe that high-dose apparently may have played a significant role in this event.

There is no consensus on the optimal timing of leukapheresis after G-CSF administration. However, it is mostly started on day 4 or 5, or even as early as day 3.[16] Studies have shown that the peak number of circulating CD34+ cells is usually reached on day 5 or 6 of G-CSF use in normal subjects.[17,18] In the case presented above and from the report by Dincer AP *et al.,*[11] apheresis was carried out after completion of 5-day course of G-CSF at 20 μg/kg/day (day 6) aiming at collecting maximum number of CD34+ cells with a single procedure. From these two experiences it would be fair to say that late conduction of apheresis after high-dose G-CSF use might also be a contributing factor to the increased risk of splenic rupture as it results in prolonged exposure of the donor to high doses of G-CSF. Further studies are needed to determine optimal timing of apheresis in relation to dose of G-CSF.

Splenomegaly is a common feature in patients treated with G-CSF.[19,20] Splenic size is observed to increase markedly between day 4 to 6 of G-CSF treatment and return to normal several days after discontinuation of treatment.[19] Apheresis, generally carried out between days 3 to 6 of G-CSF treatment, coincides with the period at which the spleen is markedly enlarged and therefore more prone to injury. This time sequence might

explain why most reported cases of splenic rupture occur within the days of apheresis and beyond (day 6 in our case). The exact mechanism of the splenic tissue enlargement and spontaneous splenic rupture remains unclear. It is thought to be secondary to mechanical effect of distension due to: i) intrasplenic accumulation of circulating granulocytes and myeloid precursors; ii) extramedullary myelopoiesis; iii) intrasplenic trapping and proliferation of stem cells.[20]

Although regarded as safe and well tolerated, G-CSF administration could result in potentially fatal complications, even in healthy individuals. Therefore, it should be used with caution and close monitoring of recipients (including close monitoring of vital signs, abdominal physical examination, daily complete blood count test and abdominal ultrasound or computed tomography when necessary) during and several days after G-CSF treatment is recommended. Recipients should be informed about this and other potentially fatal complications and advised to avoid vigorous activities, as mild trauma could result in injury in an already fragile spleen. Finally, early timing of apheresis (day 3, 4 or at most 5) should be considered particularly when administering high-dose GCSF.

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