



## Case report

# Life-threatening capillary leak syndrome after G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation

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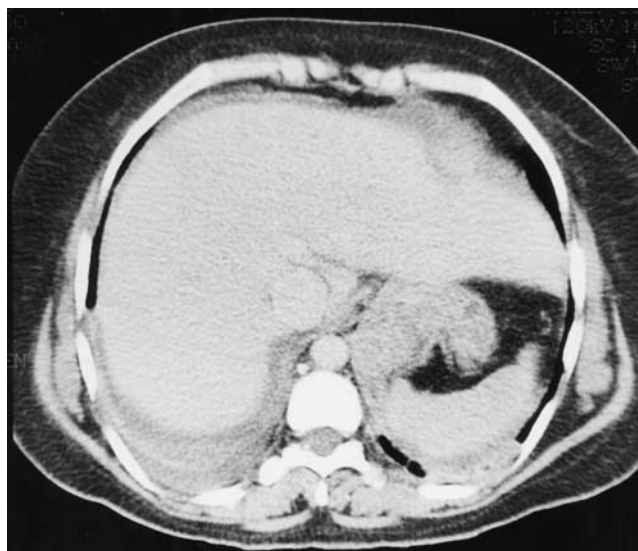
### Summary:

**We report a case of capillary leak syndrome in a 37-year-old female PBPC donor who received G-CSF 900  $\mu\text{g}/\text{day}$  for 4 days and underwent leukapheresis. This lady had remained well and stable despite marked leukocytosis during G-CSF treatment, but developed hypotension during leukapheresis, quickly followed by hypoxemia, ascites, pericardial and pleural effusion, shock, edema, neurologic changes and hepatocellular injury. Upon G-CSF withdrawal, dopamine and crystalloid infusion, methylprednisolone treatment and suspension of apheresis, the clinical situation fully reversed. We hypothesize that leukapheresis, in the presence of marked leukocytosis and high doses of G-CSF, may have triggered neutrophil activation and the release of inflammatory mediators, resulting in tissue damage and systemic manifestations of increased capillary permeability. *Bone Marrow Transplantation* (2001) 28, 311–312.**

**Keywords:** G-CSF; capillary leak syndrome; leukapheresis; peripheral blood progenitor cell transplantation

A 37-year-old white female agreed to donate allogeneic G-CSF-mobilized PBPC for her brother. She was asymptomatic, in good health, and used no medications. Her past medical history was unremarkable. Physical examination was normal except for moderate obesity and bradycardia. She had a normal chest film and echocardiogram. ECG showed sinus bradycardia. Serum biochemistry and coagulation tests were normal, Hb was 12.9 g/dl, hematocrit 38%, WBC  $6.4 \times 10^9/\text{l}$  (ANC  $3.1 \times 10^9/\text{l}$ ) and platelets  $322 \times 10^9/\text{l}$ . She received G-CSF 900  $\mu\text{g}$  s.c. daily in two divided doses for 4 days (10  $\mu\text{g}/\text{kg}/\text{day}$ ). On the fifth day, the WBC count was  $90.5 \times 10^9/\text{l}$ . Her only symptom thus far had been moderate headache which subsided with acetaminophen. A last dose of G-CSF was given. Three hours after the start of apheresis, she was pale and hypotensive, complaining of respiratory discomfort, nausea and weakness. Intravenous

saline and calcium gluconate were given, with partial improvement. Apheresis was stopped after 5 h and she received another dose of G-CSF, because the number of CD34<sup>+</sup> cells collected had been insufficient. Returning in the next morning, she complained of dyspnea, pleuritic pain and 'tightness in the chest'. Hematocrit was 33% and WBC  $74.7 \times 10^9/\text{l}$ . Minutes later, she fainted and was admitted to the emergency room with severe hypotension, pallor, pulmonary rales, hypoxemia, cyanosis and confusion. A CT scan showed ascites, pericardial fluid and bilateral pleural effusion (Figures 1 and 2). Pericardiocentesis yielded clear fluid with 65 cells/mm<sup>3</sup> (77% neutrophils), 4.2 g/dl protein and LDH 512 U/l. Pleural fluid had the same characteristics. Her hemodynamic status improved with i.v. saline and dopamine. She remained confused and agitated for the next 12 h, normalizing her mental status gradually thereafter. A CT scan of the head was normal. Her weight was 8 kg above baseline. Her previously normal alanine aminotransferase peaked at 568 U/l (normal: <37 U/l). Bilirubin and alkaline phosphatase were unchanged. Hypoalbuminemia (3.2 g/dl) developed. Myocardial damage was ruled out by the normal electrocardiogram and serial myocardial



**Figure 1** CT scan of upper abdomen showing pleural effusion and accumulation of ascitic fluid behind the right hepatic lobe. A thin layer corresponding to the diaphragm is visible, separating both cavities.



**Figure 2** CT scan of the thorax showing pericardial and bilateral pleural effusion, more evident on the right.

enzyme measurements (CK, CK-MB) in the first 48 h after apheresis. Methylprednisolone 100 mg i.v. daily was started. Renal function tests remained normal. Polyuria ensued, and the patient lost 10 kg in the following week. Platelets fell to a nadir of  $81 \times 10^9/l$  on the 5th day post-apheresis. After 4 days, methylprednisolone was withdrawn and the patient gradually resumed her activities and was discharged with a normal CBC and biochemistries 10 days post apheresis.

## Discussion

Capillary leak syndrome (CLS), characterized by weight gain, ascites, edema and multi-organ dysfunction, including non-cardiogenic pulmonary edema with or without pleural effusion, has been described in BMT recipients at the time of stem cell infusion or hematopoietic recovery,<sup>1</sup> and in breast carcinoma and lymphoma patients recovering from high-dose therapy followed by G-CSF administration with or without PBPC support.<sup>2,3</sup> Hypovolemic shock has been shown to cause a 1.9- to 7.1-fold increase in the levels of G-CSF mRNA in the lungs of rats when compared to healthy control animals.<sup>4</sup> Using *in situ* hybridization, bronchial epithelial cells were found to be the major site of G-CSF mRNA production in the rats with lung injury, and the levels of mRNA were directly proportional to the duration of hypotension. The hypothesis that lung injury could result from locally increased levels of G-CSF and subsequent neutrophil recruitment and activation was later confirmed by intratracheal injection of G-CSF; BAL fluid and lung biopsies revealed marked edema of the interstitium and

alveoli.<sup>5</sup> Iijima *et al*<sup>6</sup> found significant increases in the rheological activity of leukocytes and serum levels of granulocyte elastase in patients receiving G-CSF as compared to those in untreated subjects. Our patient developed an acute, systemic inflammatory reaction which started during leukapheresis and culminated in serosal inflammation and effusion, hypoxemia, shock, edema, neurologic changes and hepatic injury. Pulmonary edema has indeed been reported soon after BM harvesting in a donor who had been receiving G-CSF.<sup>7</sup> In our case, despite marked leukocytosis the previous day, the patient had had few symptoms until shortly after the start of apheresis. We are not aware of any reported cases of life-threatening CLS in PBPC donors. The acute complications of G-CSF reported to occur in healthy donors have remained rare and have so far been restricted to biochemical abnormalities (hyperuricemia, elevated alkaline phosphatase), bone pain, headache, localized thrombotic phenomena and a case of splenic rupture.<sup>8</sup> In our case, we believe that apheresis, in a patient with marked neutrophilia and concomitant G-CSF stimulation may have, like BM harvesting in the case described by Kitamura *et al*,<sup>7</sup> triggered leukocyte activation and production of inflammatory mediators, resulting in widespread tissue injury and CLS, an unusual and potentially life-threatening acute complication of G-CSF-mobilized PBPC donation.

## References

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