Acute Lung Injury in a Healthy Donor during Mobilization of Peripheral Blood Stem Cells Using Granulocyte-Colony Stimulating Factor Alone

Granulocyte-colony stimulating factor (G-CSF), a hematopoietic growth factor, is widely used to accelerate recovery from neutropenia after severe chemotherapy, both decreasing the risk of infection and mobilizing peripheral blood stem cells. Adverse effects occur with G-CSF use in approximately 30% of cases, comprised predominantly of bone pain, headache, and general fatigue. Pulmonary toxicity is very rare. Here, we describe a healthy donor for allogeneic hematopoietic stem cell transplantation who developed acute lung injury (ALI) after 4 days of G-CSF administration. Among the serum cytokines examined, only Interleukin (IL)-1β level was elevated in this case. As a high level of IL-1β was detected at the onset of ALI, on day 4 after G-CSF administration, and decreased to below the level of detection on day 11, it is possible in a certain part that IL-1β was involved in the onset of G-CSF-related ALI in the present case.

Figure 1. A From day 4 of G-CSF administration, when ALI developed. Marked infiltrative shadows were apparent in bilateral lung fields, particularly in the lower lobes. B Infiltrative shadows were greatly improved from day 3 of methylprednisolone administration.

Case report
A 30-year-old man was hospitalized at our hospital as a human leukocyte antigen (HLA)-matched donor for allo-HSCT, used as treatment for his mother with adult T-cell leukemia (ATL). The patient reported no past history of respiratory or autoimmune disease. The results of chest radiography and physical examination on admission were normal. No significant abnormalities were apparent on laboratory examinations: white blood cell count (WBC), 4500/µL (neutrophils 55%, eosinophils 1%, lymphocytes 39%, monocytes 5%); red blood cell count (RBC), 479×10⁴/µL; hemoglobin concentration (Hb), 15.9 g/dL; platelet count (Plt), 20.5×10⁴/µL; serum lactate dehydrogenase (sLD), 292 IU/L; and C-reactive protein (CRP), 0.05 mg/dL. Subcutaneous administration of 5 µg/kg G-CSF (Lenograstim; Chugai Pharmaceutical Co., Japan) twice daily was initiated for PBSC mobilization.

On Day 4 of G-CSF administration, the patient developed dry cough, dyspnea, and sudden severe deterioration of blood gas levels, with PaO₂ of 53.8 mmHg in room air. No cardiac dysfunction was detected on cardiochography. PaO₂/FIO₂ was 256, compatible with a diagnosis of ALI. Emergent examination indicated leukocytosis, particularly neutrocytosis, and elevation of sLD and CRP levels: WBC, 28,900/µL (neutrophils 86%, eosinophils 1%, lymphocytes 9%, and monocytes 4%); RBC, 438×10⁴/µL; Hb, 14.8 g/dL; Plt, 15.9×10⁴/µL; sLD, 570 IU/L; and CRP, 2.90 mg/dL. Chest radiography (Fig. 1A) on Day 4 of G-CSF administration revealed marked infiltrative shadows in bilateral lung fields, particularly in the lower lobes. High-resolution computed tomography (CT) of the chest indicated diffuse ground glass opacity and fine nodular shadows (Figure 2A, B). Diagnosis of ALI attributable to G-CSF was made, and so G-CSF administration was terminated. Large doses of methylprednisolone were administered intravenously for 4 days, with 500 mg/day on the first and fourth days after diag-
concentration was 17.0 pg/mL on Day 4 of G-CSF administration, and IL-8 concentration was below the limit of detection on Day 4 of G-CSF medication, but was 5.0 pg/mL on Day 11. TNF-α concentrations were below the limit of detection at all time points examined.

**Discussion**

G-CSF is a hematopoietic growth factor that enhances proliferation of polymorphonuclear leukocytes (PMN). G-CSF, which is widely used to accelerate recovery from neutropenia after bone marrow suppressive therapy, lowers the risk of infection and may enable increases in chemotherapy dosage. With allo-HSCT, G-CSF is commonly administered to healthy donors for mobilization of PBSC. Adverse effects comprised typically of bone pain, headache, or general fatigue occur following G-CSF administration in approximately 30% of cases. In addition, adverse effects mediated by activation of the immune response after therapeutic use of cytokines have been reported. Franzke et al. provided new mechanistic insights into the immune modulatory effects of G-CSF on the T-cell immune system. Their results suggested that G-CSF acts as a strong immune regulator on T-cells and modulates T-cell immune responses directly via its receptor on T-cells. Therefore, G-CSF is an interesting candidate for specific immune modulation in transplantation, especially acute graft versus host disease (GVHD) and other pathological conditions associated with Th1/Th2 imbalance, such as bone marrow failure syndromes and Th1-mediated autoimmune diseases. Our patient did not have a past history of autoimmune disease, and did not show onset of autoimmune disease after G-CSF treatment. The ALI in the present case was not related to autoimmune disease. Reported complications include ARDS, pulmonary capillary leak syndrome, interstitial pneumonitis, and deterioration of pulmonary function in neutropenic patients with ARDS. Although the incidence of G-CSF-related pulmonary toxicities is low, such complications are serious and can be fatal. Azoulay et al. reported 84 cases with probable G-CSF-related pulmonary toxicity among 1801 patients receiving G-CSF treatment. Of these, only 2 cases involved use of G-CSF alone. The patient reported here represents a rare case of G-CSF-related pulmonary toxicity induced by G-CSF alone. The incidence of G-CSF-related pulmonary toxicity seems to increase in combination with chemotherapy. In particular, G-CSF enhances bleomycin-induced pulmonary toxicity via as yet unknown mechanisms involving neutrophils.

Sato et al. reported that G-CSF-induced PMN activation is involved in the onset of ALI. They determined circulating leukocyte counts, markers of activation on PMN, and circulating levels of G-CSF, IL-6, and PMN elastase with both single bolus and continuous subcutaneous G-CSF administration. They concluded that continuous subcutaneous injection of G-CSF resulted in marrow responses resembling those of bolus injection, but with reduced PMN activation. Healthy donors are commonly administered G-CSF at a dose of 10 µg/kg/day in either one or two doses daily. Administration of granulocyte macrophage-colony stimulating factor (GM-CSF) to healthy animals has been reported to cause alveolar cell recruitment and pulmonary edema. In the same model, intravenous or subcutaneous administration of G-CSF alone produced neither pulmonary edema nor alveolar neutrophil influx. However, both events occurred soon after instillation of G-CSF into the trachea.

In 1967, Ashbaugh et al. reported that ARDS was the result of local or systemic insults leading to diffuse alveolar damage. Subsequently, various mediators have been shown to be involved in the pathophysiology of ALI, with a complex interplay between pro- and anti-inflammatory mediators. Several studies have demonstrated that serum concentrations of several cytokines increase at the onset of ARDS, particularly IL-1β, IL-6, IL-8, IL-10, and TNF-α. However, HLA phenotypes have also been associated with onset of G-CSF-related pulmonary toxicity. Takatsuka et al. reported that patients with HLA-B51 or -B52 phenotypes display a tendency toward complications involving neutropenic infection after chemotherapy or HSCT, in association with elevation of TNF-α and IL-8 during WBC recovery. In the present...
case. IL-1β was elevated at ALI onset, but IL-8 and TNF-α concentrations were below the limits of detection. As a high level of IL-1β was detected at the onset of ALI, on day 4 after G-CSF administration, and decreased to below the level of detection on day 11, it is possible in a certain part that IL-1β was involved in the onset of G-CSF-related ALI in the present case. The etiologies of G-CSF-related pulmonary toxicity may differ between patients with chemotherapy, autologous or allogeneic HSCT, and those who have undergone G-CSF administration alone. In addition, the present patient showed neither HLA-B51 nor HLA-B52 phenotype. Complex mechanisms may underlie the relationships between HLA phenotype and ALI.

The present report described G-CSF-induced lung toxicity in a healthy donor for allo-HSCT. Allo-HSCT with use of G-CSF for mobilization will undoubtedly be performed more frequently for numerous hematopoietic diseases and cancers. G-CSF-related lung injury must therefore be considered as a possible and critical adverse event.

---

**References**


