Capillary Leak Syndrome Likely the Result of Granulocyte Colony-Stimulating Factor after High-Dose Chemotherapy

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Two cases of malignant lymphoma complicated with capillary leak syndrome following super high-dose chemotherapy and administration of granulocyte colony-stimulating factor (G-CSF) are presented. Subsequent to the nadir of granulocytes, and at the stage of rapid increase of granulocytes, the symptoms of fever, hypotension, dyspnea, pleural effusion and edema appeared, and laboratory data revealed hypoxia, hypocapnia and hypoalbuminemia. In addition, an abscess-like lesion was observed in the liver in one patient. After the administration of G-CSF was ceased or decreased, and pulse therapy with methylprednisolone was initiated, these symptoms disappeared quickly.

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Key words: chemotherapy, growth factor, dyspnea, methylprednisolone

Introduction

The use of hematopoietic growth factors which act on granulocyte and macrophage committed stem cells, i.e., granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), has been found to decrease the duration of agranulocytosis infectious episodes associated with bone marrow suppression after chemotherapy or bone marrow transplantation (1–4). Adverse effects due to these agents include rash, bone pain, weight gain, edema, pleural and pericardial effusions, and pulmonary thrombus (1–4). Rare cases of capillary leak syndrome characterized by weight gain, peripheral edema, pleural effusion, pulmonary infiltrates, hypoxia and hypotension caused by the administration of GM-CSF (1, 2, 5), interleukin-2 (IL-2) (6) and tumor necrosis factor (TNF) (7) have been reported. However, there have been no reports of capillary leak syndrome caused by G-CSF (8). We present two cases of capillary leak syndrome likely due to G-CSF, which were successfully treated by cessation or reduction of G-CSF dose and pulse therapy with methylprednisolone.

Case Report

Case 1

The patient was a 38-year-old male who was diagnosed with malignant lymphoma of the oral tonsil in May 1990. He

received autologous bone marrow transplantation on February 24, 1992, during the first remission (Fig. 1). The preconditioning regimen consisted of mitoxantrone (MIT) 7 mg/m², cytosine arabinoside (Ara-C) 1.5 g/m²/12 hours, 2 times/day, and etoposide (VP-16) 300mg/m²/day, from days –5 to –3. The administration of G-CSF, 300 µg/day by intravenous infusion was begun on day 0. On day 9, the granulocyte count began to increase. On day 11, there was pyrexia of 38°C–39°C, when the granulocytes had increased to 5.6×10⁹/L. On day 13, the patient complained of dyspnea, and pleural effusions were seen on the chest x-ray (Fig. 2). At that time, granulocytes increased to 16.2×10⁹/L, CRP was 27.0 mg/dl, PO₂ was 63.0 mmHg, and PCO₂ was 31.4 mmHg. The serum albumin level, 4.0 g/dl on day 15, decreased to 2.7 g/dl on day 18, and the hematocrit value, 44.0% on day 14, decreased to 32.6% on day 18. At this time, serial blood cultures were performed; but, no evidence of bacterial or fungal infection was found.

A diagnosis of capillary leak syndrome was made on the basis of blood gas analysis and laboratory findings. The discrepancy between serum albumin and hematocrit on day 18 was due to anemia of chemotherapy induced marrow suppression. An oxygen mask was supplied, and pulse therapy with methylprednisolone (m-PSL) was initiated. The administration of G-CSF was stopped for 2 days, with a subsequent rapid drop in granulocyte count; G-CSF was then started again at a reduced dose, on day 21. The fever dropped on day 17, pleural effusion disappeared and CRP improved to 1.4 mg/dl on day 21. Also on

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Fig. 1. Clinical course of patient 1. BMT: bone marrow transplantation, PC: platelet concentrate, LPRC: leukocyte-poor red cells, m-PSL: methylprednisolone. Methylprednisolone was administered initially at 1,000 mg/day followed by tapered doses.

Fig. 2. Chest X-ray of patient 1, 14 days after autologous bone marrow transplantation. Pleural effusions of right lung were observed.

Fig. 3. Liver computed tomography of patient 1, 21 days after bone marrow transplantation. Diffuse low density lesion of the right lobe was observed.

day 21, a low density liver lesion suggestive of an abscess appeared on computed tomography (CT) (Fig. 3). Blood chemistry findings were; total bilirubin 0.3 mg/dl, direct bilirubin 0.1 mg/dl, GOT 19 u, GPT 50 u, γ -GTP 266 u, LDH 583 u, ALK-

P 157 u, cholesterol 157 mg/dl, and blood sugar was 174 mg/dl. Liver CT findings became normal on day 31.

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Fig. 4. Clinical course of the patient 2.

Case 2

A 38-year-old male was diagnosed with malignant lymphoma of the cervical spinal cord at the C3 level on July 1991. He received radiation of 4,400 cGy and two courses of chemotherapy. He entered into complete remission and was discharged on December 1991. In November 1992, he suffered from newly appearing left hemiplegia and was diagnosed with relapse in the spinal cord at the C2 level from the magnetic resonance imaging findings. Chemotherapy was started on November 18, consisting of cyclophosphamide (CY) 1g/day, Ara-C 1g/day, from day 1 to day 5, and methotrexate (MTX) 3g/day on day 8 (Fig. 4). The administration of G-CSF, 250 µg/day by intravenous infusion was begun on day 2. On day 20, the granulocyte count began to increase. On day 21, high fever over 40°C appeared when the granulocytes had increased to $0.2 \times 10^9/L$. On day 26, he complained of edema of the bilateral lower legs and palms and hypotension. The serum albumin level, 3.3 g/dl on day 20, decreased to 2.4 g/dl on day 26, and the hematocrit value, 27.9% on day 20 decreased to 22.7% on day 26. The discrepancy between serum albumin and hematocrit was due to the bone marrow suppression after chemotherapy. On day 27, pleural effusion appeared on the chest X-ray when the granulocytes increased to $2.3 \times 10^9/L$ (Fig. 5). On day 28, he complained of dyspnea and PO_2 was 59.9 mmHg and PCO_2 was 29.4 mmHg, and CRP was 27.0 mg/dl. In this term, serial blood cultures were performed, but, no evidence of bacterial or fungal infections was found. An oxygen mask was supplied and pulse

Fig. 5. Chest x-ray of the patient 2, 27 days after chemotherapy. Pulmonary congestion and pleural effusion were observed.

therapy with m-PSL and administration of catecholamines were initiated, and the dose of G-CSF was reduced and then administration was stopped. These symptoms disappeared until day 34. The patient subsequently received a super-high dose of chemotherapy and autologous bone marrow transplantation combined with G-CSF administration. This time the patient did

not suffer from the capillary leak syndrome, and successfully recovered from bone marrow suppression.

Discussion

Capillary leak syndrome is characterized by the symptoms caused by the capillary hyperpermeability resulting in a shift of fluid and protein from the intravascular to extravascular space (9). Since our patients were critically ill when the symptoms appeared, we could not perform thoracentesis or transbronchial lung biopsy to prove the pathological nature of the disease. Repeated blood cultures for the bacterial and fungal infections were negative. The capillary leaky syndrome of our patients was probably related to the administration of G-CSF, since the disease developed at the rapid recovery phase of granulocytes and ameliorated after reduction or cessation of G-CSF. The pathophysiological mechanism of the cytokine-induced capillary leak syndrome which is characterized mainly by the respiratory distress symptoms, resulting from the increased production and excess accumulation of the leukocytes and release of cytokines in the lungs, might involve the following observations which have effects in common or which interact: 1) Vascular permeability is increased due to the endothelial damage caused by superoxide anion radicals produced by the activated and increased granulocytes (10). 2) GM-CSF increases cell to cell adhesion and the surface expression of adhesion-promoting surface glycoproteins on mature granulocytes (11, 12). GM-CSF also promotes leukocyte adherence to capillary endothelial cells and extracellular matrix, mediated by integrins (leukocyte adhesion receptors) (13). 3) Administration of GM-CSF was immediately followed by transient neutropenia, and evidence of pulmonary granulocyte sequestration was observed (14). 4) Fluid retention resulting from extravasation of intravascular fluid occurs due to the administration of TNF (7), IL-2 (6, 15), and also due to GM-CSF in which the production of TNF by macrophage is enhanced by GM-CSF (16). 5) GM-CSF activates T cells, thus causing increased IL-2 production (17). The mechanism by which G-CSF causes capillary leak syndrome is not known, and we speculate that the phenomena cited above, is the result of the increased and activated granulocytes by G-CSF administration, and the sharing of effects via the cytokine network, may be responsible for the pathogenesis. A similar situation was recently reported, when all-trans retinoic acid was used to induce leukocyte differentiation and hematological remission in patients with promyelocytic leukemia, a potentially lethal syndrome of pulmonary infiltration developed; this was usually accompanied by peripheral blood leukocytosis (18).

Sequestration and aggregation of granulocytes might also occur in organs other than the lung or skin (1–4, 14, 19–21). To our knowledge, this is the first report of an abscess-like lesion in the liver detected graphically by CT as a low density lesion probably due to the accumulation of the leukocytes, although this was not proved histologically by liver biopsy. Liver toxicity by GM-CSF was only measured by liver enzyme elevation (22).

It is not known whether these complications could also occur

in a particular situation, e.g., in the rapid recovery phase of hematopoiesis following super high-dose chemotherapy, after which bone marrow recovery is enhanced by G-CSF. In such a case, rapid mobilization of granulocytes might cause uneven distribution of the increased granulocytes in certain organs. Or, alternatively it could be merely the result of leukocytosis enhanced by G-CSF. Not all of the patients with enhanced leukocytosis by G-CSF or GM-CSF had such serious complications. These complications can also occur in patients who do not have leukocytosis (18).

Beneficial effects of dexamethasone in blocking the capillary leak syndrome have been reported in patients who received IL-2 as cancer treatment (23, 24). In our patients, methylprednisolone was effective, along with cessation or reduction of the dose of G-CSF.

The clinical features of G-CSF-induced capillary leak syndrome are distinct, and could be separated from the septicemia or bacterial pneumonia which frequently occurs during episodes of nadir of neutrophils. In the present patient, these complications disappeared soon after granulocyte count was normalized, and the intensive treatment for infection was not necessary although a regular dose of antibiotics was administered until reaching hematological stability.

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