Splenomegaly due to the use of granulocyte-colony stimulating factor

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ABSTRACT

Granulocyte-colony stimulating factor (G-CSF) is a growth factor used for stem-cell mobilization and neutropenia treatment. We report that splenomegaly was detected in a 16-years-old patient with acute lymphoblastic leukemia following the administration of G-CSF. The presence of splenomegaly in the patients receiving G-CSF may be related to the use of G-CSF.

Key Words: Splenomegaly, Colony-stimulating factor.

ÖZET

Granülosit-koloni stimüle eden faktör kullanımına bağlı splenomegali

Granülosit-koloni stimüle eden faktör (G-CSF) kök hücre mobilizasyonu ve nötropeni tedavisi için kullanılan bir büyüme faktörüdür. Bu olgu 16 yaşında ve G-CSF kullanımı ardından splenomegali gelişen bir olgu olup, splenomegali nedeninin G-CSF olduğu düşünülmektedir.

Anahtar Kelimeler: Splenomegali, Koloni-stimülan faktör.

INTRODUCTION

Granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor are glycoproteins which mediate the production, differentiation and functions of the macrophages and neutrophils. These drugs are used to achieve peripheral stem-cell mobilization in allogenic or autologous stem cell transplantation and to increase neutrophil count in neutropenic patients[1]. Muscle pain, headache, fatigue and nausea are common side effects of these drugs. The less reported side effects are fever, chills, noncardiac chest pain, local reac-

tion at the injection side, insomnia, dizziness, and low-grade fever[2]. There are several reports about splenomegaly due to the use of G-CSF[3-5]. Also, nontraumatic splenic rupture has also been reported in patients who had splenomegaly as a rare complication of G-CSF administration[6].

In this paper, splenomegaly due to use of G-CSF for peripheral stem-cell mobilization is reported in a patient with acute lymphoblastic leukemia.

A CASE REPORT

A 16-years-old patient had been admitted to a hematology center in 1997 with complaints of fatigue and rash. On his physical examination, splenomegaly had been found in addition to petechia and purpura on both lower limbs. Laboratory values were as follows: leukocyte count 70.000/µL, hemoglobin 13.6 g/dL, hematocrit 42.6%, platelet count 8.000 /µL. On peripheral smear, the ratio of the cells estimated 48% for blast cells, 38% for neutrophils, and 14% for lymphocytes. In the bone marrow, 76% of the cells observed were blastic. The morphology of blastic cells was homogenously monomorphic and had a loose chromatin network without vacuoles. The patient had been found periodic-acid schiff positive and peroxidase negative. The percentage of CD10 in bone marrow on the flow cytometry had been found to be 30%, CD5 93%, CD7 78%, CD19 3%, CD20 1%, CD22 3%, CD3 18%, CD33 2%, CD13 2% and HLA-DR 8% and ALL-L_2 had been diagnosed. ALL-BFM-95 protocol had been started and complete remission had been achieved using this treatment protocol[7]. The patient was admitted to our hospital for follow-up in 2002. Physical examination was normal without organomegaly as well as the results of whole blood count and peripheral smear. On bone marrow aspiration and biopsy, there were normocellularity, three cellular lines with normal maturation, 1/4 ratio erythroid/myeloid ratio and no blastic cells. Before stem cell collection, the patient was considered as complete remission and cryo-preservation was planned to prevent the recurrence. For stem-cell mobilization, a regimen consisting of cyclophosphamide 2.4 g/m^2 plus mesna 2.4 g/m^2 plus G-CSF 5 µg/kg was applied[8]. At day 9, leukocyte count was 22.900/µL, monocyte count 1.557/µL, and CD34 25.6/µL. 4.49 x 10^6/kg CD34 positive stem cells were collected. In the next day, the physical examination was normal except 4 cm splenomegaly. The longitudinal diameter of the spleen was 13 cm by the ultrasonography. Liver function tests, erythrocyte and platelet counts were normal. *Brucella* and *Salmonella* agglutination tests, antibodies to hepatitis B and C virus, Epstein-Barr virus viral capsid antigen, *Toxoplasma* IgM and cytomegalovirus IgM were negative. Splenomegaly spontaneously disappeared after 7 days the cessation of G-CSF.

DISCUSSION

G-CSF increases the neutrophil count in the circulation and myeloid cells in the bone marrow by shortening the time for differentiation from the stem cell to mature neutrophil. Granulocyte proliferation was observed in the red pulp of the enlarged spleen in rats on the fifth day of the G-CSF treatment. In the studies on rats, it was found that thymidylate synthase (TS) and thymidine kinase (TK) mRNA's in splenic cells were significantly increased after 6 hours of G-CSF. It was also found that TK and TS activities increased approximately 5 days after G-CSF application to the bone marrow. It explains the probable cause of splenic rupture[9].

Furthermore, there were extramedullary myelopoesis without any disruption on the erythroid and megakaryocytic cells in the red pulp of the spleen on the histological examination of splenic rupture after G-CSF administration in a patient[10]. Platzbecker et al found that the mean increases were 11 mm and 5 mm in longitudinal and transvers diameters of spleen by ultrasonography in 91 healthy donors using 7.5 µg/kg G-CSF for peripheral stem cell mobilization, respectively[3]. Donadieu et al administered 5-20 µg/kg per

day G-CSF to 19 patients with severe chronic neutropenia[4]. Neutrophil recovery was achieved in all patients and splenomegaly was observed on 2 (10.5%) patients. In another study, splenomegaly was observed in 12 of 54 patients with congenital or cyclic neutropenia[5].

In the study by Picardi et al G-CSF was administered to 22 patients and 13 healthy controls[11]. Splenomegaly was detected in 6 (17%) patients by palpation, by ultrasonography-measured longitudinal diameter in 21 (60%) patients and by ultrasonography-calculated volume of spleen in 32 (91%) patients. So ultrasonography-calculated volume of spleen had been suggested for the detection of splenic enlargement. In this study, splenic enlargement had been found to correlated with increase in the white blood cell but not with that of circulating CD34 positive cells.

In the meta-analysis of three studies, splenic enlargement was increased from 6-15% at baseline to 15-31.8% on treatment with use of G-CSF in 1027 patients with idiopathic, cyclic and congenital severe chronic neutropenia. When computed tomography and magnetic resonance imaging, was used splenomegaly sustained at 18 months and decreased toward pretreatment values at 2.5 years[12].

In addition to G-CSF induced splenomegaly, spontaneous splenic rupture may be seen at 6th and 10th days of the treatment in patients administered G-CSF for peripheral stem cell mobilization[2,10,13].

Our patient received G-CSF in a dose of 5 μg/kg/day for 9 days. Splenomegaly was detected at 10th day of the treatment. It has been reported in the literature that splenomegaly due to G-CSF application may be seen between at 6th and 10th days of the treatment. We observed splenomegaly only in this one of 19 patients received G-CSF for stem-cell mobilization in our clinic.

G-CSF is a growth factor used for stem-cell mobilization and neutropenia treatment. Differential diagnosis of splenomegaly is important for the underlying disease especially leukemias and lymphomas. It should be remembered that the presence of splenomegaly in the patients receiving G-CSF may be related to the use of G-CSF.

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