Case Report

Gynecol Obstet Invest 1995;40:276–277

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Effective Treatment of Drug-Induced Agranulocytosis Using Recombinant Human Granulocyte Colony Stimulating Factor in Pregnancy

Key Words
Drug-induced agranulocytosis
Granulocyte colony stimulating factor
Pregnancy, drug-induced agranulocytosis

Abstract
Drug-induced immune system mediated agranulocytosis is a rare but potentially life-threatening condition. There have been only a few reports on the drug-induced agranulocytosis during pregnancy. We present a case of agranulocytosis after prolonged intravenous infusion of ritodrine hydrochloride and additional administration of indomethacin suppositories, effectively treated using recombinant human granulocyte colony stimulating factor without any infection in a mother with twin-to-twin transfusion syndrome. Recombinant human granulocyte colony stimulating factor may have a potential use for drug-induced agranulocytosis during pregnancy.

Introduction

Drug-induced immune system mediated agranulocytosis is a rare but potentially life-threatening condition. This complication of drug therapy occurs usually within the first 3 months of treatment and is characterized by a sudden drop of the granulocyte count to almost 0. Nearly all patients develop severe septicemia with or without localized infection and rare critically ill. Following withdrawal of the offending drug, the granulocyte count returns to normal within 1 to several weeks [1]. There have been only a few reports on drug-induced agranulocytosis during pregnancy [2]. To the best of our knowledge, there has been no report on the use of recombinant human granulocyte colony stimulating factor (G-CSF) in the treatment of drug-induced agranulocytosis during pregnancy. We describe a case of agranulocytosis after prolonged intravenous infusion of ritodrine hydrochloride and additional administration of indomethacin suppositories, effectively treated using G-CSF without any infection in a mother with twin-to-twin transfusion syndrome.

Case Report

A-26-year old Japanese woman, gravida 2, para 2, was admitted to our university hospital for premature labor due to twin-to-twin transfusion syndrome at 22 weeks of gestation. She was begun on a regimen of a continuous intravenous infusion of ritodrine, varying from 0.1 to 0.2 mg/min, but contractions did not cease. Therefore, she received additional indomethacin suppositories, varying from 50 to 150 mg/day. Amniocentesis (four times) was performed for relief of abdominal pain and discomfort, and the total amount of amniotic fluid removed was 6,600 ml.

On admission, the white blood cell count was 6,900/mm^3 with 55% segmented neutrophils, 32% lymphocytes, and 10% monocytes. Hemoglobin was 9.0 g/dl, and the platelet count was 229,000/mm^3. On the 23rd hospital day, the white blood cell count eventually

Received:
February 27, 1995
Accepted:
March 27, 1995

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0378–7346/95/0404–0276
$8.00/0

dropped to 1,600/mm^3 with 0% segmented neutrophils, 0% band forms, 52% lymphocytes, 46% monocytes, and 2% basophils. Hemoglobin was 8.7 g/dl, and the platelet count was 310,000/mm^3. Bone marrow examination showed hypocellularity with a lack of late granulocyte forms. Ritodrine and indomethacin were discounted, and broad-spectrum antibiotic treatment was started. In addition, G-CSF (Sankyo, Tokyo, Japan; 1.5 g/kg/day s.c.) was started. Two days after G-CSF administration, the white blood cell count was 2,700/mm^3 with 0% neutrophils and rose to 7,100/mm^3 with 13% neutrophils, 5% bands, 42% lymphocytes, 26% monocytes, and 1% basophils 5 days later. On physical examination no splenomegaly was noted, and no sites of infection were identified. The next day (29 weeks of gestation) she was delivered vaginally of 2 viable female infants weighing 960 and 740 g, respectively. The complete blood counts in the 1st (recipient) baby were 7,700/mm^3 for white blood cells, 20.4 g/dl for hemoglobin, and 212,000/mm^3 for platelets, and those in the 2nd (donor) baby were 8,900/mm^3 for white blood cells, 14.7 g/dl for hemoglobin, and 180,000/mm^3 for platelets. The maternal white blood cell count was 11,800/mm^3, with 21% neutrophils, 7% bands, 23% lymphocytes, and 25% monocytes. On day 8 G-CSF was stopped. The patient had an uneventful puerperal course, and no postpartum infectious complications occurred.

Discussion

The diagnosis of drug-induced agranulocytosis was made on the basis of the clinical findings [1]. In this report, the patient was simultaneously exposed to two drugs (ritodrine and indomethacin) which are known to induce agranulocytosis [2, 3]. It must be stated that definite proof that ritodrine and/or indomethacin caused the agranulocytosis in our patient is lacking, since serological testing was not done. However, leukopenia and neutropenia resolved rapidly within 7 days after cessation of both drugs.

Treatment with G-CSF has two beneficial effects: (1) shortening of the duration of complete agranulocytosis and (2) an accelerated increase of granulocytes during the recovery phase [1]. It cannot be proved that G-CSF treatment was responsible for the rapid recovery of granulocytes; however, there are several arguments which suggest that G-CSF treatment may have shortened the duration of agranulocytosis [1]. The time to recovery is strongly dependent on the number of granulocyte precursors in the bone marrow. If the bone marrow is hypoplastic, the duration of agranulocytosis ranges from 7 to 56 (median 14) days. In our patient the bone marrow immediately before the start of G-CSF therapy was hypoplastic; therefore, it might be expected that a recovery time is >7 days. However, in our patient, neutrophils recovered (normalization of neutrophil count >1,500/mm^3) within 7 days. Wang-Cheng and Davidson [2] reported that leukopenia and neutropenia resolved very rapidly within 3 or 4 days after cessation of ritodrine without the use of G-CSF. The reason for this difference of recovery time is currently unknown. One possible explanation is that granulocyte precursors in the bone marrow in their case might be present in normal numbers, although these authors did not perform bone marrow examination.

Maternally administered G-CSF has been shown to cross the placenta and induce a peripheral neutrophilia in fetal rats [4]. In our case, the white blood cell counts in both babies were within normal ranges. The reason for this unresponsiveness to G-CSF in our babies is currently unknown. However, time and dose of G-CSF during pregnancy might affect the effect of G-CSF on fetal granulopoiesis.

References

1 Willfort A, Lorber C, Kapiotis S, Sertl S, Hainz R, Kirchweger P, Jäger U, Kyrle PA, Lechner K, Geissler K: Treatment of drug-induced agranulocytosis with recombinant granulocyte colony-stimulating factor (rhG-CSF). Ann Hematol 1993;66:241–244.

2 Wang-Cheng R, Davidson BJ: Ritodrine-induced neutropenia. Am J Obstet Gynecol 1986;154:924–925.

3 Millington M: Leucopenia and indomethacin. Br Med J 1966;i:49.

4 Medlock ES, Kaplan DL, Cecchini M, Ulich TR, Castillo JD, Andresen J: Granulocyte colony-stimulating factor crosses the placenta and stimulates fetal rat granulopoiesis. Blood 1993; 81:916–922.