Drug-induced thrombocytopenia during G-CSF therapy in a patient with chronic neutropenia

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ABSTRACT

A one-year-old infant presented with recurrent perianal abscesses and pneumonia, and was diagnosed with chronic neutropenia. Treatment with granulocyte colony-stimulating factor (G-CSF) was initiated, and thrombocytopenia was detected three weeks later. The drug was discontinued but the patient's platelet count did not improve. A short course of high-dose methylprednisolone was administered, and both the platelet and neutrophil counts returned to normal. Based on this response, in order to maintain the neutrophil count the steroid treatment was continued for one year with tapered doses. At the time of writing, the patient had been doing well for 13 months without treatment. This report highlights that G-CSF treatment for severe chronic neutropenia in a child may be associated with thrombocytopenia.

Key Words: G-CSF, Thrombocytopenia, Children, Neutropenia.

ÖZET

Kronik nötropenili bir hastada G-CSF tedavisi sırasında gelişen ilaca bağlı trombositopeni

Tekrarlayan perianal apseler ve pnömoni ile getirilen bir yaşındaki bir süt çocuğuna kronik nötropeni tanısı konuldu. Granülosit koloni stimüle edici faktör (G-CSF) başlandıktan üç hafta sonra hastanın trombositopenisi saptandı. İlacın kesilmesine rağmen hastanın trombosit sayısı düzelmedi. Bir kür kısa süreli yüksek doz metilprednizolon verilince hem trombosit hem de nötrofil sayısı normale döndü. Hastanın tedaviye verdiği bu cevaba dayanarak, nötrofil sayısını aynı düzeyde tutmak için steroid tedavisi bir yıl süreyle azaltılarak verildi. Yazının yazıldığı sırada, hasta 13 aydır tedavisiz ve sağlıklı olarak izlenmektedir. Bu vaka, ağır kronik nötropenisi olan bir çocukta G-CSF tedavisinin trombositopeni katkısı olabileceğini göstermektedir.

Anahtar Kelimeler: G-CSF, Trombositopeni, Çocuk, Nötropeni.

INTRODUCTION

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor that regulates the proliferation and maturation of neutrophil progenitors. Use of this agent in children with severe chronic neutropenia leads to markedly higher numbers of neutrophils, which helps reduce infectious complications. These effects have increased the survival rate in this patient group[1-4]. G-CSF is considered to be a relatively safe drug that sometimes produces mild adverse effects of bone pain, splenomegaly and thrombocytopenia. These conditions are transient, and they usually cease when G-CSF treatment is stopped[1-4].

In this paper, we describe the case of an infant with chronic neutropenia who developed thrombocytopenia while on G-CSF therapy.

A CASE REPORT

A 24-month-old boy presented with a perianal abscess that had first been noted 12 days earlier. The infection had been investigated at another center, where leukopenia and neutropenia were both detected at two examinations done seven days apart. The child was referred to our hospital because of severe neutropenia. His medical history revealed an earlier perianal abscess at 15 months of age, and two bouts of pneumonia at 16 and 23 months of age, respectively. The family history was unremarkable.

On admission, the patient weighed 13.5 kg (75^{th} percentile) and was 96 cm tall (90^{th} percentile). He had a fever of 38.9°C and a red, painful, indurated 2 cm-diameter mass in his perianal region. The child did not have splenomegaly. Findings in other systems were normal. Laboratory investigations revealed hemoglobin 10.2 g/dL, hematocrit 29.4%, white blood cell count (WBC) 4.7 x 10^9/L, and platelet count 305 x 10^9/L. The differential count showed 83% lymphocytes, 7% neutrophils, 8% monocytes, and 2% eosinophils. Anisocytosis and hypochromia were also detected. The absolute neutrophil count (ANC) was 0.309 x 10^9/L. A smear of bone marrow aspirate showed arrest of myeloid maturation, and normal megakaryocyte number and morphology with a differential of 2% promyelocytes, 30% myelocytes, 10% metamyelocytes, 25% normoblasts, 7% eosinophils, 24% lymphocytes, and 2% monocytes. Bone marrow cytogenetic analysis showed normal karyotype (46, XY). Serological tests for cytomegalovirus, Epstein-Barr virus, hepatitis A, B and C viruses, rubella virus, Parvovirus B19, human immunodeficiency virus, *Toxoplasma* spp., *Salmonella* spp., and *Brucella* spp. were all negative. No bacterial growth was observed in cultures of blood, urine, and nasopharyngeal material. The baby's serum levels of vitamin B12 and folic acid were within normal limits. The serum levels of iron (18 ng/dL) and ferritin (25 ng/dL), and the transferrin saturation index (4.0%) were compatible with iron deficiency anemia. Serum levels of immunoglobulin A, G, and M were normal.

In light of the bone marrow findings and the patient's age, the initial diagnosis was chronic neutropenia and iron deficiency anemia. In addition to antibiotic therapy and surgical drainage of the abscess, subcutaneous G-CSF treatment was started at a dose of 5 μg/kg/day. Seven days after G-CSF was initiated, the ANC had risen to 2.0 x 10^9/L. Response to the therapy implied that neutropenia was transient. At three weeks, the ANC remained stable above 1.5 x 10^9/L, but the baby's platelet count was markedly reduced (87.0 x 10^9/L). By four weeks after the start of G-CSF, the platelet count had dropped further to 17.0 x 10^9/L. At this stage, we lowered the G-CSF dose to 2 μg/kg/day, and then it tapered further to 0.5 μg/kg/day over the following two weeks. However, the platelet count did not rise. At the same time, the patient became symptomatic, exhibiting significant ecchymosis in all body regions and occult hemorrhage at the injection sites. He was given oral iron sulfate treatment started after antibiotic treatment in order to treat iron deficiency anemia.

Based on the persistence of thrombocytopenia despite reduction of the G-CSF dose, we stopped administering G-CSF and obtained another bone marrow aspirate. The smear showed hypercellular bone marrow with a differential count of 3% promyelocytes, 18% myelocytes, 30% metamyelocytes, 20% neutrophils, 10% lymphocytes, 5% eosinophils, and 14% normoblasts. Increased numbers of megakaryocytes were noted. Meanwhile, no microbiological agent was detected by cultures and serological tests. We waited two weeks to gauge the effect of G-CSF interruption. However, the child's platelet count remained at 6.0-28.0 x 10^9/L and his symptoms persisted. During the stoppage of G-CSF, the patient developed no infection even though his ANC remained between 0.6 and 1.1 x 10^9/L. Further serological testing was done, and the results for autoimmune markers (direct antiglobulin test, antinuclear antibody, anti-DNA antibody, anticardiolipin antibody, lupus anticoagulant, and complement-3 and complement-4 levels) were all negative. The evidence from bone marrow examination, the patient's drug history, and the lack of improvement in platelet count despite stoppage of G-CSF suggested G-CSF–induced autoimmune thrombocytopenia.

Steroid therapy was initiated with a short course of high-dose methylprednisolone (30 mg/kg/day for 3 days, 20 mg/kg/day for 4 days). Then slow stepwise tapering of the steroid dose was begun. The patient responded well, with no adverse effects. By the end of the first seven days on steroid therapy, his platelet count had risen to 136 x 10^9/L, his WBC had risen to 10.5 x 10^9/L, and his ANC was 3.3 x 10^9/L. The beneficial effect on the neutrophil count compelled us to continue steroid treatment at 2 mg/kg/day. We decreased the dose by 0.5 mg/kg every three days in order to keep the ANC above 0.5 x 10^9/L. One year later, the steroid treatment was stopped. Meanwhile, no adverse effect related to steroid therapy was observed. At a check-up approximately 13 months after steroid therapy was stopped, the patient was healthy and had completely normal hematological findings.

DISCUSSION

The introduction of G-CSF as therapy for children with severe chronic neutropenia has considerably changed the management protocols for this patient group. Prior to the development of this agent, the focus was symptomatic treatment of complications. Administration of G-CSF results in effective resolution of neutropenia and helps prevent infectious episodes. The first large series that explored G-CSF treatment for chronic neutropenia in childhood revealed a few mild adverse effects, and indicated that dose reduction or withholding of the drug leads to complete recovery from any such effects[1]. Nevertheless, in cases of long-term treatment of chronic neutropenia with G-CSF, concerns began to arise about development of problems such as secondary myelodysplastic syndrome/acute myeloblastic leukemia, vasculitis and glomerulonephritis, and abnormal growth and development[2,3].

Our case identifies another side effect of G-CSF therapy, namely, autoimmune thrombocytopenia. In line with the proposed criteria for chronic neutropenia, we diagnosed this condition based on the baby's five-month history of recurrent perianal abscesses and pneumonia, and his persistently low ANC (< 0.5 x 10^9/L)[4]. The patient was prescribed G-CSF therapy, and thrombocytopenia developed three weeks later. We suspect that our patient's thrombocytopenia was a drug-induced immune reaction. In this condition, antibodies bind to platelet glycoproteins in the presence of certain drugs or their metabolites, and cause destruction of platelets. In drug-induced immune thrombocytopenia, the thrombocytopenia is preceded by treatment with the suspected drug, and the platelet abnormality resolves after the agent is discontinued[5-9]. According to the literature, the majority of patients with G-CSF-associated thrombocytopenia recover completely when the drug dosage is reduced or therapy is stopped altogether[1-3]. In our

case, however, G-CSF preceded thrombocytopenia but neither dose reduction nor withholding of G-CSF led to recovery. A given agent may also induce or be associated with autoimmune thrombocytopenia. In this phenomenon, immune destruction of platelets continues despite discontinuation of the responsible agent[7,9]. In our case, the increased numbers of megakaryocytes in the bone marrow suggested immune destruction. We found no other potential cause of thrombocytopenia, and observed dramatic resolution of the problem after steroid treatment; thus, we identified G-CSF-induced autoimmune thrombocytopenia as the most likely diagnosis in this case.

Due to the severity of the child's symptoms, we administered a short course of high-dose methylprednisolone as treatment for autoimmune thrombocytopenia. In the first week of this therapy, the baby's ANC and platelet count both rose. We believed that re-exposure to G-CSF would result in thrombocytopenia, and decided to continue with tapering doses of methylprednisolone to maintain the ANC above 0.5 x 10^9/L. One case report has described successful treatment of chronic neutropenia with steroid therapy alone[10]. Although the mechanism is not fully understood, Dror et al.[11] have suggested that glucocorticoids may exert their effects in chronic neutropenia by acting directly on the signal transducer and activator of transcription (STAT) proteins that are linked to G-CSF receptors[11].

In conclusion, this case report highlights that children being treated for severe chronic neutropenia may develop G-CSF-induced thrombocytopenia. In our patient, steroid treatment resulted in complete resolution of the thrombocytopenia and neutropenia. This case underlines the importance of considering drug-induced thrombocytopenia as a possible complication of G-CSF treatment. Awareness of this risk may facilitate early diagnosis and treatment of similar cases.

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