Spontaneous remission of granulocyte colony-stimulating factor–associated leukemia in a child with severe congenital neutropenia

Sima Jeha, Ka Wah Chan, Andrew G. Aprikyan, W. Keith Hoots, Steven Culbert, Hallie Zietz, David C. Dale, and Maher Albittar

Leukemia is observed with increased frequency in patients with severe congenital neutropenia (SCN). In the past decade, recombinant human granulocyte colony-stimulating factor (rh G-CSF) has prolonged the survival of patients with SCN increasingly reported to have leukemias. In this communication acute myelogenous leukemia (AML) associated with a mutation of the G-CSF receptor (G-CSF-R) developed in a patient with SCN maintained on long-term G-CSF therapy. The blast count in the blood and bone marrow fell to undetectable levels on withholding G-CSF and without chemotherapy administration, but the mutant G-CSF-R was detectable during this period. The patient subsequently underwent successful allogeneic bone marrow transplantation. After transplantation, the patient’s neutrophil elastase (ELA-2) mutation and G-CSF-R mutation became undetectable by polymerase chain reaction. This report provides novel insights on leukemia developing in congenital neutropenia. (Blood, 2000; 96:3647-3649)

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Introduction

Severe congenital neutropenia (SCN), first described by Kostmann in 1956, is a disorder of myelopoiesis characterized by impaired neutrophil differentiation with maturation arrest at the promyelocyte stage.1,2 The resultant profound neutropenia usually leads to fatal infections early in infancy, but in a few instances it has remitted or has been mild enough to allow prolonged survival. Transition to leukemia has been reported in 3 patients who survived through adolescence with no cytokine treatment.3-5 Bone marrow transplantation was the only effective therapy to prolong the survival of patients with SCN6-7 until granulocyte–colony-stimulating factor (G-CSF) was introduced.8,9 However, an apparent increase in the incidence of leukemia has also been observed in the past few years.11,12 This phenomenon could be related to prolonged survival of children who have a preleukemic disorder, thus allowing the disease to follow its natural course. Prolonged hematopoietic stimulation with G-CSF has also been suggested to contribute to the development of leukemia.13,15 We present a patient with SCN in whom acute myelogenous leukemia (AML) developed after 9 years of G-CSF treatment. The leukemia remitted spontaneously with the discontinuation of G-CSF alone, allowing the patient to receive a successful unrelated bone marrow transplant without the morbidity of induction chemotherapy.

Study design

M.P. is a 12-year-old boy who received a diagnosis of severe neutropenia at the age of 3 months. There is no family history of consanguinity or hematologic disorders. During the first 3 years of his life, he was admitted to the hospital more than 30 times for life-threatening infections. At age 3, G-CSF treatment was begun, and the patient was maintained on 5 µg/kg subcutaneously twice a day. He responded excellently to G-CSF, allowing him to lead a normal life for 9 years. On March 17, 1999, a surveillance bone marrow aspirate was within normal limits with a diploid male karyotype (46,XY) in 20 metaphases. On June 8, 1999, severe left otitis associated with extensive cellulitis developed on the left side of the face. Complete blood count showed hemoglobin 11.0, platelets 153 000, white blood cell count 11 800, and 32% myeloperoxidase-positive blasts. Bone marrow aspirate confirmed the diagnosis of AML with 73% blasts, myeloperoxidase positive, CD34 97.5%, CD13 92.6%, and CD33 31.4%. Cytogenetics assay showed a pseudodiploid clone 46,XY, add (18) (q23), in 18 metaphases and a diploid male karyotype 46,XY in 2 metaphases. G-CSF was discontinued, and the patient begun treatment with intravenous antibiotics. After 5 days, the infection had markedly improved and the white blood cell count gradually decreased. Because of the patient’s stable clinical condition and the clearance of circulating blasts, the decision was made not to begin chemotherapy and to continue withholding G-CSF while maintaining close observation and prophylactic antibiotics. After 4 weeks without G-CSF, a repeat bone marrow aspirate documented complete morphologic and cytogenetic remission that lasted for 11 weeks, at which time the family declined bone marrow transplantation and restarted the patient on 3 µg/kg G-CSF twice a day to maintain his absolute neutrophil count in the 1000 range. A surveillance bone marrow aspirate taken 7 weeks after G-CSF was restarted showed 40% myeloperoxidase-positive blasts with reappearance of the old 18q+ clone and a new clone with trisomy 21. G-CSF administration was interrupted again, and the patient achieved a second remission in 14 days without chemotherapy. After 6 weeks in complete remission, he underwent matched, unrelated bone marrow transplantation. Six months after transplantation, the leukemia remains in remission. Cytotoxicity assays, flow cytometry studies, and cytokenetic analysis were performed on bone marrow aspirates using standard methodology.16 Neutrophil elastase (ELA-2) and granulocyte colony-stimulating factor receptor (G-CSF-R) were analyzed by polymerase chain reaction (PCR) and reverse transcription (RT)-PCR using genomic DNA and RNA, respectively. All 5 exons for ELA-2 were sequenced as previously reported. The result demonstrated a mutation at position 109 in the neutrophil elastase (ELA-2) associated with a mutation of the G-CSF receptor (G-CSF-R). The mutation is a deletion of the single nucleotide at position 109 in the elastase (ELA-2) gene that is codominantly inherited by the patient's parents. The result suggested that the patient's neutrophil elastase (ELA-2) and G-CSF-R mutation is a genetic marker for his neutropenia and leukemia. The patient subsequently underwent successful allogeneic bone marrow transplantation. After transplantation, the patient's neutrophil elastase (ELA-2) mutation and G-CSF-R mutation became undetectable by polymerase chain reaction. This report provides novel insights on leukemia developing in congenital neutropenia.
November 1, 0146,XY, add (18)(q23), i(21)(q10)(5)
sequenced.

binding, the G-CSF-R is dimerized and stimulates cell proliferation
from the 3-month remission period (Table 1).

G-CSF, but a mutation of G-CSF-R was detectable in 2 samples
morphologic and cytogenetic remission on discontinuation of
abnormality after 9 years of treatment with G-CSF. The patient had
elastase, AML developed in association with a clonal cytogenetic
manifests the recently reported mutation of the gene for neutrophil
with SCN. In this patient, who has had SCN since infancy and who

Results and discussion

Although it allows a dramatic improvement in quality of life and
survival, the prolonged use of G-CSF in children with SCN has
been associated with adverse side effects that vary in severity.16 In
some cases, it is difficult to determine whether the complications
are associated with the underlying pathophysiology of the disease,
are induced by G-CSF, or are related to a combination of both.

The greatest concern is the risk for hematopoietic malignancies.
In these patients, treatment is difficult and most patients die within
a few months despite the use of aggressive chemotherapy.19-22 The
latest report from the Severe Chronic Neutropenia International
Registry indicates that the incidence of myelodysplastic syndrome
and AML is almost 9% in patients with SCN receiving G-CSF.23
Malignant myeloid disorders have not been reported11,18 in patients
with idiopathic or cyclic neutropenia maintained on long-term
administered with G-CSF. The mechanism that allowed this patient’s
leukemia to remain quiescent when pharmacologic doses of G-CSF
were withdrawn deserves further study. The G-CSF-R mutation persisted
although a second morphologic remission was achieved 14 days after
G-CSF was again stopped, and it lasted until the patient underwent
bone marrow transplantation 6 weeks later. After transplantation,
both the elastase and the G-CSF-R mutations were no longer
detectable (Table 1). The G-CSF expansion of the blast count in this patient
is consistent with models in which selection and maturation of
individual hematopoietic lineages are stimulated by hematopoietic
growth factors. The mechanism that allowed this patient’s leukemia
to remain quiescent when pharmacologic doses of G-CSF were
withdrawn deserves further study. The G-CSF-R mutation persisted

The case we present here is the first to demonstrate a direct
relation between G-CSF administration and blast count in a patient
with SCN. In this patient, who has had SCN since infancy and who
manifests the recently reported mutation of the gene for neutrophil
elastase, AML developed in association with a clonal cytogenetic
abnormality after 9 years of treatment with G-CSF. The patient had
morphologic and cytogenetic remission on discontinuation of
G-CSF, but a mutation of G-CSF-R was detectable in 2 samples
from the 3-month remission period (Table 1).

G-CSF is known to mediate its effect by G-CSF-R. On ligand
binding, the G-CSF-R is dimerized and stimulates cell proliferation
or differentiation by activating various signaling pathways.24
Current evidence25 indicates that mutations in G-CSF-R lead to
hypersensitivity to G-CSF with robust proliferation of the host
cells. In this patient, we examined bone marrow by PCR and
RT-PCR using G-CSF-R–specific primers. Sequencing of the


table 1. blast counts and cytogenetics performed on bone marrow aspirations while patient was on and off G-CSF

<table>
<thead>
<tr>
<th>Date (1999)</th>
<th>G-CSF µg/kg/d</th>
<th>Blasts (%)</th>
<th>Karyotype</th>
<th>NE/ELA-2</th>
<th>G-CSF-R</th>
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<tr>
<td>March 17</td>
<td>10</td>
<td>5</td>
<td>46,XY (22)</td>
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<td>Normal</td>
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<tr>
<td>June 8</td>
<td>10</td>
<td>73</td>
<td>46,XY, add (18)(q23)(18)</td>
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<td>Abnormal</td>
</tr>
<tr>
<td>July 2</td>
<td>0</td>
<td>2</td>
<td>46,XY (20)</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>August 26</td>
<td>0</td>
<td>1</td>
<td>46,XY (20)</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>October 18</td>
<td>6</td>
<td>40</td>
<td>46,XY, add (18)(q23)(4)</td>
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<td>Abnormal</td>
</tr>
<tr>
<td>November 1</td>
<td>0</td>
<td>1</td>
<td>46,XY, add (18)(q23), i(21)(q10)(5)</td>
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<td>Abnormal</td>
</tr>
<tr>
<td>November 29</td>
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<td>1</td>
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<td>Abnormal</td>
</tr>
<tr>
<td>Post-transplantation day 100</td>
<td>0</td>
<td>1</td>
<td>46,XX(20)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

7. Pahwar RN, O’Reilly RJ, Broxmeyer HE, Smithwick EM, Pahwa SG, Kapadia A. Partial


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