CASE REPORT

Spontaneous Remission in Hypoplastic Acute Leukemia

Masahiro Kizaki, Tetsuhei Ogawa, Yonosuke Watanabe*
and Keisuke Toyama**

Department of Internal Medicine, School of Medicine, Keio University
Tokyo, Japan
*Department of Pathology, School of Medicine, Keio University
Tokyo, Japan
**The First Department of Internal Medicine, Tokyo Medical College
Tokyo, Japan

(Received for publication on March 31, 1988)

Abstract

A recurrent spontaneous complete remission of acute hypoplastic leukemia was observed. The remission occurred after a severe infection which was treated with antibiotics. Reports of spontaneous remission of acute leukemia in adults have become increasingly rare, and the remissions themselves are short-lived. Such spontaneous complete remissions are almost always associated with bacterial infections and blood transfusions. Previous cases are summarized, and the pathophysiologic factors are discussed.

Key words: acute leukemia, spontaneous remission, infection

Introduction

Spontaneous remission of acute leukemia is a rare event. Since 1955, a few cases have been reported. This decrease in frequency reflects the use of more strict criteria...
for complete remission and the advance of combination chemotherapy. Most of these cases had normo or hypercellular marrow at the diagnosis of acute leukemia. However, recurrent remission in hypoplastic leukemia was rare. We report here one case of hypoplastic acute leukemia with recurrent spontaneous hematological regression.

Fig. 1 Bone marrow biopsy sections, stained by hematoxylin-eosin (10×40). a: Obtained at the diagnosis of acute hypoplastic leukemia in November 1983. b: Obtained at relapse of acute leukemia in July 1985. At this time, the bone marrow shows hypercellular marrow with a lot of blast cells.
Case Report

A 53-year-old female was admitted to [blank] Hospital in November 1983 complaining of fever and oral ulcer. She had previously been well with no history of a recent injection nor exposure to drugs or toxins. Physical examination revealed no abnormalities but severe anemia. The leukocyte count was 700/µl with 18% blast cells. Hemoglobin was 8.5 g/dl and platelet count was 21.6×10⁴/µl. Serum transaminase and alkaline phosphate levels were normal, as were prothrombine and partial thromboplastine times. Erythrocyte sedimentation rate (ESR) was 90 per hour, and fibrinogen was 460 mg/dl. Bone marrow biopsy revealed hypocellular marrow with 65% blasts (Fig. 1-a). These blasts had no cytoplasmic granules and Auer rods. The nucleus was almost round shaped and had some large nucleoli (Fig. 2). Electron microscopic studies demonstrated that these cells had high nuclear-cytoplasmic (N/C) ratio and the nucleus had an obvious nucleolus and few chromatins (Fig. 3). The cytoplasm contained no granules. Cytochemical analysis showed that myeloperoxidase (MPO) and platelet peroxidase (PPO) activity could not be detected in blast cells. Various surface markers were not positive except for Ia antigens. Cytogenetic analysis showed normal karyotype. From these findings, a diagnosis of acute hypoplastic leukemia was established.

Fig. 2 Bone marrow aspirate at the time of diagnosis. Blast cell shows no cytoplasmic granules and Auer rods. The nucleus is almost round shaped and has some large nucleoli (10×100).
Massive antibiotic therapy combining gentamicin (GM) and piperacillin (PIPC) was begun. The patient's temperature was recovered to normal over the first week of observation. All cultures were negative. The infection began to respond the aggressive measures from June, 1984, and simultaneously, the patient's leukocyte started to increase (Fig. 4). Bone marrow examination performed on August 1 revealed that blasts were normal in number and fulfilled the criteria for complete remission.

She was discharged from the hospital in excellent physical condition. After 5 months, her bone marrow began to show replace by leukemic cells and her peripheral leukocyte count fell to 1,300/µl with 43% blasts. At this time, she also had a high fever but cultures were negative. Administration of antibiotics was begun. This time also she responded to antibiotic therapy and her temperature returned to normal range. Consequently, a complete remission was achieved again without any antileukemic chemotherapy on February 5, 1985. The bone marrow still showed hypocellularity, with less than 5% blasts and without qualitative abnormalities. Peripheral blood was normal.

Five months after her second spontaneous remission, her leukocyte count in-
Spontaneous Remission in Acute Leukemia

Fig. 4 Clinical course of this patient.

creased up to 11,400/µl with 89% blasts which were peroxidase-negative, α-naphthyl acetate esterase-negative and PAS negative. Her hemoglobin level was 9.9 g/dl and platelet count was 51,000/µl. The bone marrow biopsy yielded hypercellular marrow (Fig. 1-b), with 87% blasts. A diagnosis of acute leukemia in relapse was made.

Because of progressive increase in blast cells, an induction treatment was started on August 5. Chemotherapy consisted of doxorubicin (ADR) 30 mg per day on days 1, 8 and 15; vincristine (VCR) 2 mg per day on days 1, 8 and 15; and prednisolone (PSL) 40 mg per day for days 1 through 15. However, complete remission was not achieved. Then she received cytosine arabinoside (Ara-C), 80 mg per day for days 1 through 7; ADR 30 mg per day on days 1, 8 and 15; vindesine (VDS) 2 mg per day on days 1, 8 and 15; methotrexate (MTX) 20 mg per day on days 8, and 15; and PSL 30 mg per day for days 1 through 15. During the hypoplastic phase after chemotherapy, the patient died of septicemia due to Pseudomonas aeruginosa on November...
Discussion

It is of interest that this patient with acute hypoplastic leukemia recovered from a life-threatening infection by antimicrobial antibiotic therapy and achieved a simultaneous remission of acute leukemia.

Eisenlohr\(^1\) reported the first case of spontaneous remission of a "marked leukocytosis" following an acute typhoid infection. Until 1955 about 100 such cases were recorded.\(^2\) Although not all of these cases were well-documented, findings of these cases stressed the role of infections and transfusions. Since 1955, only 10 cases of spontaneous remission in adult acute leukemia have been reported (Table 1). The definition of complete remission in acute leukemia became more strict.\(^3\) Moreover, the early institution of chemotherapy has improved the complete remission rate. From

### Table 1  Cases of Spontaneous Complete Remissions Reported since 1955

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>(FAB) Type</th>
<th>Associated infection</th>
<th>Leukocyte transfusions</th>
<th>Complete remission duration (M)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiernik(^5)</td>
<td>22/F</td>
<td>ALL</td>
<td>Escherichia coli sepsis</td>
<td></td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40/M</td>
<td>AML</td>
<td>pneumonia empyema</td>
<td></td>
<td>4-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25/M</td>
<td>AML</td>
<td>α-Streptococcus + aerobacter peritonsillar abscess</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75/M</td>
<td>AMoL</td>
<td>pneumonia</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17/F</td>
<td>AMoL</td>
<td>E. coli peritonitis</td>
<td></td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Lachant et al(^8)</td>
<td>67/F</td>
<td>AML</td>
<td>pneumonia</td>
<td>(+)</td>
<td>17</td>
<td>RAEB→AML aleukemic</td>
</tr>
<tr>
<td>Ifrah et al(^7)</td>
<td>56/M</td>
<td>AML (M1)</td>
<td>pneumonia</td>
<td>(+)</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18/M</td>
<td>AML</td>
<td>(−)</td>
<td>(−)</td>
<td>2</td>
<td>hypoplastic</td>
</tr>
<tr>
<td>Yamao et al(^9)</td>
<td>52/M</td>
<td>APL (M3)</td>
<td>Fourrier's gangrene of scrotum</td>
<td>(+)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Raza et al(^11)</td>
<td>53/F</td>
<td>AL</td>
<td>fever of unknown origin</td>
<td>(−)</td>
<td>5,  (1st CR)</td>
<td>hypoplastic</td>
</tr>
<tr>
<td>This report</td>
<td></td>
<td>AL</td>
<td></td>
<td>(−)</td>
<td>5, (2nd CR)</td>
<td></td>
</tr>
</tbody>
</table>

AML: acute myelogenous leukemia  AL: acute leukemia  
APL: acute promyeloctic leukemia  RAEB: refractory anemia with excess of blasts  
ALL: acute lymphoblastic leukemia  CR: complete remission
these reasons, the number of patients with spontaneous remission became progressively fewer.

It is suggested from previous cases that these remissions did not lead to increase in survival which might exceed six months. However, in the well documented case reported by Ifrash et al. the patient had spontaneous remission which lasted for 34 months. This is the longest remission period under such a situation. However, as our case, there were no cases in recurrent spontaneous remission of acute hypoplastic leukemia.

A pathophysiologic features of spontaneous remission in acute leukemia remain hypothetical. A review of the literature showed that several cases of spontaneous remission from acute leukemia were accompanied by severe life-threatening infections. It was therefore proposed that nonspecific stimulation of the immune system by infection might play a major role in inducing remission. Therefore, attempts were made to manipulate the immune system artificially by such techniques as injection of malarial parasites, or the use of M. tuberculosis, Coley toxin, glandular fever or feline panleukemia virus. All attempts to replicate remission induction by infection have consistently failed heretofore. Pseudomonas vaccination has been correlated with an increased rate of complete remission, but had no influence upon its duration. Non-specific immunotherapy using bacterial extracts has been shown by several trials to be of limited value in prolonging duration of remission or survival period. However, one of the most frequent effects of immunotherapy using BCG is the achievement of consecutive remission after relapse. This can be related to observations showing that mycobacteria enhances GM-CSF differentiation. Moore et al. have recently proposed that differentiating factors can be released after the injection of endotoxin. In these years, it has been reported that various agents such as 13-cis-retinoic acid or 1.25-dihydroxy vitamin D3 induce differentiation of leukemic cells. In our case, during therapy for infection the patient did not receive any vitamin, steroidal therapy or any other drugs besides antibiotics. Therefore, induction differentiation and maturation by agents can be neglected.

The next possible remission in acute leukemia is transfusions. The possible anti-leukemic effect of lymphocytes contained in fresh blood or leukocyte transfusions has been advocated by Schwarzenberg et al. They observed a higher rate of complete remission in patients presenting a graft-versus-host (GVH) reaction following leukocyte transfusions. An antileukemic effect has also been attributed to GVH reaction following allogenic bone marrow transplantation with reduced risk of relapse. However, there was only one case that complete remission could be obtained after leukocyte transfusions without any GVH reaction. In such a case, natural killer activity, antibodies against leukemic cells and the roles of soluble factors such as colony stimulating activity have been evoked to explain the remission following fresh blood or
leukocyte transfusions.

Including our case, the latest cases\textsuperscript{6,7,23} had atypical factors such as hypoplastic leukemia or smoldering leukemia. From this point of view, one may hypothesize that these leukemia cells with a slow proliferative activity could differentiate more easily, similar to what was observed with the HL-60 cell line.\textsuperscript{25} Finally, only the combination of opportunities and constitutional characteristics may lead an acute leukemia to a spontaneous remission.

This article is dedicated to Dr. Tadashi Inoue, Professor of Surgery, School of Medicine, Keio University and this patient, his late wife Mrs. Seiko Inoue.

References


