Megakaryocyte Proliferative Disorder in Neonates with Down’s Syndrome


Department of Pediatrics, National Children's Hospital, Tokyo, Japan
* Department of Pediatrics, National Saitama Hospital, Saitama, Japan
** Department of Pathology, School of Medicine, Keio University, Tokyo, Japan
*** Saitama Cancer Center, Saitama, Japan

Introduction

An intriguing hematological disorder is seen in neonates with Down’s syndrome (DS). Although this disorder clinically and hematologically resembles acute leukemia, it is reported that most of patients spontaneously regressed over weeks or months, except for some cases which lead to leukemic progression. This type of disorder is termed transient leukemoid reaction, transient abnormal myelopoiesis, or transient myeloproliferative disorder, etc. Rosner et al. (1972) speculated that “ineffective regulation of granulopoiesis, erythropoiesis, and perhaps thrombopoiesis in patients with DS could produce a hematological picture which was similar to acute leukemia.” Cosson et al. (1974) reported a case of acute megakaryocytic leukemia (FAB, M7) in a neonate with DS, and a number of similar cases have been reported subsequently. Cytogenetic abnormalities of chromosome 21 have been associated with some cases of M7 patients. However it is not confirmed that the abnormalities of chromosome 21 are specific for M7. In this paper, we discuss four newborn patients with DS, who developed transient myeloproliferative disorder (TMD) that showed megakaryocytic proliferation.

Case Reports

Case 1

A seven-day-old boy was admitted because of abdominal distension and respiratory distress. He had Down’s triad, and miliary sized erythematous rash all over his body.
The liver extended 4.5 cm and the spleen 1.0 cm below the respective costal margin. His hematologic data were as follows: hemoglobin (Hb) 18.5 g/dl, WBC 289,000/cu mm with 94.5% blasts; platelets 660,000/cu mm. No chemotherapy was given because of the diagnosis of TMD associated with DS. At the age of ten days, he developed acute renal failure due to acute blastic cell lysis. The blood cell counts returned to normal within three weeks, but thereafter pancytopenia developed. He also developed hepatic failure and a bleeding tendency like DIC. At the age of 41 days he died. At autopsy, microscopic examination revealed mild fibrosis of bone marrow and hepatic necrosis. No leukemic infiltration was found.

Case 2

A ten-day-old boy was admitted because of prolonged jaundice. He had Down’s triad. The liver was palpable 3.0 cm below the right costal margin and the spleen was not felt. His hematologic data were as follows: Hb 17.4 g/dl; WBC 28,200/cu mm with 35.5% blasts; platelets 87,000/cu mm. Bone marrow aspirate was slightly hypocellular with 41.8% replacement by blasts. No chemotherapy was given, because these findings were considered to be TMD associated with DS. His physical condition was well, and at the age of two months the blood cell counts returned to normal. Mild liver dysfunction was noted from the age of 30 days, but improved about one month later. He is now two and a half years old, remaining clinically and hematologically normal.

Case 3

A seven-day-old girl was admitted because of a heart murmur. Ventricular septal defect was revealed by ultrasonic cardiography. Other abnormal findings included Down’s triad, and the liver and spleen extended 3.0 cm and 0.5 cm below the respective costal margins. Her hematologic data were as follows: Hb 14.5 g/dl; WBC 11,000/cu mm with 17% blasts; platelets 36,000/cu mm. No chemotherapy was given because of the diagnosis of TMD associated with DS. At the age of 36 days the blasts disappeared, and thrombocytopenia resolved at the age of 50 days. She is hematologically normal at the age of five months.

Case 4

A five-day-old girl was admitted because of cyanosis and a heart murmur. The diagnosis of endocardial cushion defect was made. She also had Down’s triad and jaundice. The liver extended 3.5 cm below the right costal margin. The spleen was not felt. Her hematologic data were as follows: Hb 18.7 g/dl; WBC 16,300/cu mm with 23% blasts; platelets 172,000/cu mm. No chemotherapy was given because of the diagnosis of TMD associated with DS. The blasts disappeared within three weeks, and she is hematologically normal at the age of three and a half months.
Materials and Methods

Morphology and cytochemical studies:

Blood smears were treated with May-Giemsa stain. Cytochemical stainings for peroxidase, naphthol AS-D chloroacetate esterase, alpha-naphthyl acetate esterase, alpha-naphthyl butyrate esterase, beta-glucuronidase, acid phosphatase, periodic acid-Schiff, and sudan black B were performed.

Ultrastructural studies:

Peripheral blood cells from the four patients were studied by ultrastructural morphology, and the cytochemical techniques of myeloperoxidase (MPO) and platelet peroxidase (PPO) were employed in three patients (Case 1, 2 and 4). These techniques are detailed elsewhere. Cells were then processed by conventional electron microscopic technique.

Blood was cultured for 24 hrs without phytohemagglutinin (PHA) and the cells were analyzed with the regular Giemsa staining and Q-banding method. However, blood was cultured for 72 hr with PHA only in Case 4.

Surface marker studies:

Monoclonal antibodies, AN 51, TP 80, Plt-1, and KOR-P77 which reacts with platelet associated antigens, and other antibodies were used in Case 3 to analyze the immunological phenotype.

Results

Morphology and cytochemical studies:

In all four cases, blasts had a high nuclear cytoplasmic ratio, a round of oval nucleus with moderately fine chromatin and several distinct nucleoli, and deeply basophilic cytoplasm. Some of them showed cytoplasmic blebs. Immature megakaryocytes were also found. They had relatively large and pale basophilic cytoplasm, in which vacuoles and a few fine granules were found. Many giant platelets were also found in all four cases.

Results of cytochemical reactions are shown in Table 1. About a half of the blasts were alpha-naphthyl acetate esterase positive (NaF sensitive) in Cases 1 and 2. A majority of blasts were acid phosphatase (Tartrate sensitive) and beta-glucuronidase positive in all four cases.

Ultrastructural studies:

In Cases 1, 2 and 4, promegakaryoblasts were identified by PPO positivity in a nuclear envelope and rough endoplasmic reticulum. The various levels of maturation from promegakaryoblast to mature megakaryocyte were also recognized. After pro-
megakaryocyte, alpha granules, dense granules, and demarcation membrane systems (DMS) appeared in the cytoplasm.

The method of peroxidase reaction was not carried out in Case 3, so “undifferentiated” or “lymphoid” blasts were seen. However, alpha granules, dense granules, and DMS were recognized in some of them, so that it was thought that they belonged to the megakaryocytic lineage.

A few myeloblasts and/or lymphoblasts were found in addition to the cells in the megakaryocytic lineage in Cases 1, 2 and 4.

Cytogenetic studies:

The results are shown in Table 2. No additional karyotypic abnormality was found.

Surface marker studies:

A surface marker study was made only in Case 3. The results are shown in Table 3. Some 30% of mononuclear cells separated from peripheral blood expressed platelet associated antigens.
Megakaryocytic Leukemia

Table 3 Surface Marker Analysis of Case 3

<table>
<thead>
<tr>
<th>1. Rosette formation (Microtest Plate Method)</th>
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<tbody>
<tr>
<td>En: 50.4%</td>
<td>EA: 22.3%</td>
<td>EAC: 28.1%</td>
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</table>

2. Cell surface antigen

<table>
<thead>
<tr>
<th>KOR-Ia17 (Anti-Ia)</th>
<th>23.7%</th>
<th>OKT3</th>
<th>40.4%</th>
<th>B4</th>
<th>6.7%</th>
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<tbody>
<tr>
<td>KOR-P77 (Anti-platelet)</td>
<td>21.9%</td>
<td>OKT4</td>
<td>37.5%</td>
<td>My4</td>
<td>11.2%</td>
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<tr>
<td>Plt-1 (Anti-platelet)</td>
<td>8.0%</td>
<td>OKT8</td>
<td>9.6%</td>
<td>My7</td>
<td>9.9%</td>
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<tr>
<td>TP80 (Anti-Gp IibIIa)</td>
<td>30.7%</td>
<td>OKT11</td>
<td>44.1%</td>
<td>My9</td>
<td>13.3%</td>
</tr>
<tr>
<td>AN51 (Anti-Gp Ib)</td>
<td>35.8%</td>
<td>B1</td>
<td>4.4%</td>
<td>J5</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Discussion

Megakaryocytic proliferation was studied in TMD of 4 newborn patients with DS by ultrastructural and surface marker studies. In Case 1, 2 and 4, maturation from promegakaryoblast to mature megakaryocyte was observed.

It is thought that the proliferation of megakaryocytes in our cases was a transient reactive phenomenon due to ineffective regulation of hematopoiesis in DS, since it disappeared spontaneously and the cytogenetic analysis of cells showed no karyotypic abnormality except for trisomy 21. However, possibilities, that the proliferation of megakaryocytes was malignant and then spontaneous remission occurred cannot be denied completely. The differentiation of these benign or malignant aspects of proliferation should be clarified in future studies.