Transient Leukemoid Proliferation of the Cytogenetically Unbalanced +21 Cell Line of a Constitutional Mosaic Boy

By David C. Heaton, Peter H. Fitzgerald, G. Jan Fraser, and George D. Abbott

A newborn without any signs of Down’s syndrome was found to have an acute leukemoid proliferation that remitted without drug therapy. Chromosomal analysis of blood, bone marrow, and skin cells revealed that the child was a constitutional mosaic with normal cells and a low number of cells in which one no. 21 chromosome was replaced by a probable isochromosome for the no. 21 long arm: 46,XY/46,XY,i(21q). The abnormal cell line of the mosaic appeared to be selectively involved in this proliferation.

CONGENITAL leukemia presents at birth or shortly afterwards. It is a rare event that was first described some 60 yr ago.1 Congenital acute leukemia is commonly myeloid in type and is usually fatal.2 In some instances, however, a proliferation of immature blood cells that is clinically and hematologically indistinguishable from congenital acute leukemia undergoes a spontaneous remission after a period of weeks or months.3,4 This transient leukemoid reaction appears to be exclusive to infants with Down’s syndrome.5 We report such a leukemoid proliferation in a newborn who had no signs of Down’s syndrome. However, cytogenetic studies showed that he was a constitutional mosaic with normal cells and a minority cell line carrying, in effect, three no. 21 chromosomes as in Down’s syndrome.

CASE HISTORY

A male child was born to a 20-yr-old part Maori primipara after an estimated 39 wk gestation. The pregnancy was uneventful and the baby was delivered vaginally after 3.5 hr labor. The baby was of normal appearance, but he weighed only 2180 g. Extensive pediatric examination did not reveal any clinical signs of Down’s syndrome, nor was there any clinical suspicion of leukemia. The mother’s blood group was A Rh (D) positive and the baby’s group was AB Rh (D) positive with a negative direct Coomb’s test. The baby’s serum bilirubin was normal, and serology titers against toxoplasma, cytomegalovirus, and rubella were not elevated in mother or baby. Routine examination of the cord blood suggested a diagnosis of acute undifferentiated leukemia. This leukemic cell line underwent spontaneous remission by the time the child was 1 mo old. He had received no treatment apart from oral iron and, at the age of 1 mo, a transfusion of 75 ml of blood from a female donor. He was last seen at 6.5 mo of age at which time his weight was 7.8 kg, his height was 65.5 cm, and psychomotor development was judged to be normal. There was no lymphadenopathy, hepatosplenomegaly, or other evidence of leukemia.

RESULTS

Hematology

Cord blood showed a mild anemia with a white cell count of 42 x 10^9/liter with 58% blasts (neutrophils 18%; lymphocytes 20%; monocytes 2%; basophils 2%) and a nucleated red cell count of 4.6 x 10^9/liter. The neutrophil alkaline phosphatase score was 245. There was a moderate thrombocytopenia. A bone marrow aspirate from the right posterior iliac crest of the child at 3 days showed increased cellularity with reduced megakaryocyte numbers, normal erythropoiesis, and a normal lymphocyte number. Normally maturing myeloid cells were plentiful, but 30% of the marrow cells were blasts. These were nucleolated cells with scanty pale blue cytoplasm and no sign of granulation. The blasts were weakly positive for acid phosphatase stain, but negative for periodic acid Schiff (PAS), sudan black, myeloperoxidase, alpha naphthylacetate esterase, and naphthyl AS-D chloroacetate esterase stains. Blasts in the peripheral blood did not possess surface immunoglobulin nor did they form rosettes with sheep red cells. The blasts were classified as undifferentiated. A second marrow from the child at 13 days showed depressed erythropoiesis and there were still 30% blasts present. By 33 days, the marrow had returned to normal with a blast count less than 1%. The blast count in the peripheral blood fell steadily, and these cells disappeared from the blood during the first month of life (Fig. 1). The platelet count also became normal.

Bone Marrow Culture

Bone marrow cells from the initial aspirate were cultured in agar using human placental conditioned medium as a source of colony-stimulating factor.6 The bone marrow showed 28 colonies/10^5 nucleated white cells (normal range 10–100 colonies). The colony incidence and colony/cluster ratio, and the absence of background single cells suggested a normal growth pattern, although this pattern is not inconsistent with some nonmyeloid leukemias.

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Peripheral blood results: hemoglobin, total leukocyte count, blast cell count, platelet count. The blast cell count and total leukocyte count share the same parameter.

**Cytogenetics**

Blood from the 3-day-old infant was cultured separately for 24 and 48 hr without mitogenic stimulation, and the cells were prepared for cytogenetic study by standard procedures and Giemsa banding. All metaphase cells in both cultures had 46 chromosomes, but one no. 21 was replaced by a metacentric chromosome consisting of two no. 21 long arms. This was most probably an isochromosome for the long arm of chromosome no. 21 (Fig. 2). The karyotype was unbalanced and had in effect three no. 21 chromosomes. Unbalanced cells with the isochromosome were also found in unstimulated blood from the child when 25 days old, but only normal metaphase cells were found in unstimulated blood cultures from the age of 52 days (Table I).

Blood cells from the child, when cultured with the mitogen phytohemagglutinin (PHA), showed a predominance of normal metaphases (Table I). Unbalanced cells with the isochromosome were present in cultures from most sample dates but appeared to fall off in frequency with increased age of the child.

A bone marrow aspirate taken from the 3-day-old child and prepared for cytogenetic examination by a direct method without culture showed a mixture of normal cells and unbalanced cells with the isochromosome (Table I). The findings of later marrow samples were consistent with this first result, although few metaphase cells could be scored. A fibroblast culture established from the first bone marrow aspirate showed the two cell types again with a predominance of normal cells (Table I). The four metaphases obtained from the colony-forming cells had normal karyotypes.

Two biopsies of skin were successfully cultured. Two separate fibroblast cultures were established from the second sample. There was a predominance of normal cells in all samples but some unbalanced cells with the isochromosome were present (Table I).

Blood lymphocytes from the child's mother were cultured with PHA and showed a normal female karyotype in 10 cells examined. The child's father was not available for chromosome study.

**DISCUSSION**

The blood picture of our patient was considered to be comparable with other reported cases of transient leukemoid reaction in patients with Down's syndrome.
Fig. 2. Giemsa-banded metaphase from blood taken from the 3-day-old child and cultured for 24 hr without PHA. One no. 21 chromosome is replaced by a metacentric chromosome (arrowed) that is probably an isochromosome for the no. 21 long arm. The karyotype is 46.XY. -21. +i(21q).

Table 1. The Numbers of Normal (46, XY) and Abnormal (46, XY, -21, +i(21q) Karyotypes Found in Cultured Blood Cells, Bone Marrow, and Skin Fibroblasts at Different Ages of the Child

<table>
<thead>
<tr>
<th>Age (Days)</th>
<th>Blood, Unstimulated</th>
<th>Blood + PHA</th>
<th>*Bone marrow, skin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>i(21q)</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>(24 hr)</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>(48 hr)</td>
<td>0</td>
<td>14</td>
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<td>11</td>
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<tr>
<td>194</td>
<td>10</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

*BD, bone marrow, direct preparation; CU, colony forming units—cells; BF, fibroblasts from agar cultures of bone marrow cells; SF, fibroblasts from cultured skin.
although he was clinically without Down's syndrome. His bone marrow was not packed with blasts, but there were considerable numbers both in the marrow and in the blood. These blasts could not be classified with confidence as either lymphoblastic or myeloblastic and were considered to be undifferentiated. The infant had no associated condition that might explain the abnormal hematologic findings. All signs of his blood disorder had disappeared after 1 mo.

Cytogenetic studies demonstrated two significant features. First, the child was a constitutional cytogenetic mosaic. This was established from the presence of normal cells and cytogenetically unbalanced cells in three separate tissues: bone marrow, lymphocytes, and skin. The unbalanced cell line had three no. 21 chromosomes, two of them joined and presenting as an abnormal metacentric element. This cell line represents a known karyotype of Down's syndrome. The fact that the child had a normal habitus without any sign of Down's syndrome is consistent with the large numerical predominance of normal cells. Constitutional mosaicism of normal cells and cells with this abnormal karyotype is most simply explained by the formation of an isochromosome for the long arm of chromosome 21 [(i(21q)) in one cell product of the first or a later division of a normal 46XY zygote cell. This form of mosaicism is rare, but it has been reported before in patients with a normal phenotype or with atypical Down's syndrome.

The second feature was that the leukemoid proliferation appeared to involve selectively the cytogenetically unbalanced cell line. Evidence of the leukemoid proliferation in the blood and bone marrow disappeared over the first month, and it was only during this time that cells carrying the abnormal metacentric chromosome were found in mitogenically unstimulated blood. A higher frequency of the cytogenetically abnormal cells was also evident in PHA-stimulated blood and possibly in bone marrow during this time. The very low number of chromosomally abnormal cells found in these tissues after 1 mo would appear to reflect the low grade of constitutional mosaicism and was consistent with the ratio of normal to abnormal cells found in cultures of skin cells. The leukemoid proliferation was not associated with any additional locally acquired chromosomal change like those that characterize clones in many forms of acute leukemia. The proliferation of chromosomally normal cells in mitogenically unstimulated blood samples taken at 52 days and later may reflect adjustment of the normal blood cell population following the decline of the leukemic phase.

It would appear that the transient leukemoid proliferation of our patient was a function of those hemo-

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able variation of chromosome abnormality that is similar to that found in other human acute leukemias. The nature of transient leukemoid proliferation in Down’s syndrome remains problematical. The cases of congenital leukemia that remit spontaneously and those that have an early fatal outcome are not distinguished from each other during the early leukemic phase, but only by their history. The transient proliferations are probably not true leukemias, and it has been suggested that in Down’s syndrome there may be an intrinsic, intracellular defect in the regulation of white cell multiplication and maturation that is related to trisomy of chromosome no. 21. The blood of a neonate with Down’s syndrome may respond excessively to relatively minor stimuli with a myeloproliferation resembling acute leukemia but which is self-limiting.23 The findings of our patient can be readily interpreted according to this hypothesis. It was only his chromosomally unbalanced cells that exhibited irregular granulopoiesis. His chromosomally normal cells were apparently unperturbed. The failure to find chromosomally abnormal clonal cell lines associated with the transient leukemic-like proliferations of Down’s syndrome, if substantiated by further studies, would also support the hypothesis. However, we would emphasize that the terminology used is not so important as the undoubted relevance these cases have for an understanding of the nature of leukemia.4

ACKNOWLEDGMENT

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REFERENCES

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