Transient Leukemoid Reaction and Trisomy 21 Mosaicism in a Phenotypically Normal Newborn

By Garrett M. Brodeur, Gary V. Dahl, Dorothy L. Williams, Robert E. Tipton, and David K. Kalwinsky

Transient leukemoid reactions that resemble acute leukemia have been well described for infants with trisomy 21 (Down syndrome). We report a phenotypically normal 3-day-old boy with hepatosplenomegaly, leukocytosis, and circulating myeloblasts. On chromosome analysis, trisomy 21 was found in all blood and bone marrow cells. However, only 4% of cultured skin fibroblasts were trisomic and the other 96% were normal, thus indicating mosaicism. Without treatment, the leukocyte count gradually returned to normal and the organomegaly diminished. Subsequently, chromosome analysis of blood and bone marrow disclosed a predominance of cells with a normal karyotype. These findings suggest that mosaicism could be responsible for the transient leukemoid reactions in some newborns—i.e., the trisomic cells may temporarily gain a proliferative advantage over the normal cells, perhaps by inhibiting their growth. Serial cytogenetic studies, as well as chromosome analysis of more than one tissue, may help to distinguish transient leukemoid reactions from acute leukemia in infants.

Acute leukemia occurs with increased frequency in newborns with Down syndrome. In contrast to that of later childhood, the predominant type of leukemia in infancy is myeloblastic. Conditions that appear identical to acute myeloblastic leukemia, but spontaneously resolve, are not unusual in infants with Down syndrome. While some consider these conditions to be acute leukemia that remits without treatment, others contend that they are transient leukemoid reactions. The mechanism responsible for spontaneous resolution is unclear, but may be related to an inherent abnormality in some patients with Down syndrome, since it is exceedingly rare in normal newborns. We present a phenotypically normal infant with trisomy 21 mosaicism who had a transient leukemoid reaction that resembled acute myeloblastic leukemia. Serial cytogenetic studies of several types of cells provided useful information about the spontaneous resolution of this child's disease.

Materials and Methods

Cytogenetic studies of blood were done with a modification of the technique of Moorhead et al. Cultures of blood lymphocytes were incubated overnight without phytohemagglutinin (PHA) and for 72 hr with PHA stimulation. Bone marrow studies were done according to a modification of the technique of Tjio and Whang. Fibroblasts were grown from a skin biopsy specimen and harvested for cytogenetic analysis after 33-51 days in culture. A modification of the trypsin-Giemsa technique of Seabright was used for the chromosome banding of all preparations.

Case Report

A 3-day-old white boy was referred to St. Jude Children's Research Hospital (SJCRH) for evaluation of acute myeloblastic leukemia. His mother was a 24-yr-old white woman (gravida V, para IV, aborta O), and the pregnancy, labor, and delivery were uncomplicated. There was no blood group incompatibility or evidence of congenital infection. A complete blood count was done on his second day of life when excessive bleeding developed after circumcision. The leukocyte count was $160 \times 10^9$/liter with 60% blasts that resembled myeloblasts. The patient was then referred to SJCRH for further evaluation.

On admission to SJCRH, he had a normal appearance and was in no acute distress. Abnormal physical findings included an enlarged liver, palpable 4 cm below the right costal margin, and an enlarged spleen, palpable 5 cm below the left costal margin. An erythematous papular rash on the face, chest, and lower extremities was consistent with erythema toxicum. Laboratory data included a hemoglobin of 15.9 g/dl, and a leukocyte count of $136 \times 10^9$/liter with 19% neutrophils, 3% lymphocytes, 8% eosinophils, and 70% myeloblasts. The platelet count was $242 \times 10^9$/liter and the reticulocyte count was 3%. The bone marrow aspirate was hypercellular with 50% replacement by primitive cells that resembled myeloblasts and reacted with peroxidase, Sudan Black, and specific esterase stains. These clinical and cytologic findings were consistent with a diagnosis of acute myeloblastic leukemia.

Since newborns with acute leukemia frequently have Down syndrome, he was examined carefully for the characteristic features. The facial appearance, hands, feet, and dermatoglyphics were all normal. Radiographs were also normal except that the acetabular angle was $17^\circ$—2 standard deviations below the mean value for newborns. Chromosome analysis disclosed trisomy 21 in all cells from the bone marrow and in all cells from blood incubated with and without PHA. Five days later, a skin biopsy was done and the patient's fibroblasts were cultured for later chromosome analysis.

Although he was phenotypically normal, the cytogenetic findings suggested that the patient had Down syndrome. Since leukemic conditions sometimes resolve spontaneously in these patients, no chemotherapy was given. Anemia and thrombocytopenia developed during the first month. Transfusions with packed red cells were required, but other complications, such as hemorrhage or infection, did not develop. Within 2 mo, the blood counts had returned to normal.

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normal and the organomegaly had diminished. Based on the cytogenetic study of cultured fibroblasts that were obtained earlier, the child had mosaicism for trisomy 21 (47 trisomic and 96% normal cells).

By the time he was 3 mo old, the organomegaly had almost disappeared. The hemoglobin at that time was 9.4 g/dl and the leukocyte count was 8800 x 10^9/liter with 50% neutrophils, 40% lymphocytes, 7% monocytes, 2% eosinophils, 1% basophils, and no blasts. The platelet count was 406 x 10^9/liter. After 72-hr PHA stimulation, 76% of blood lymphocytes had a normal karyotype, and 24% had the 47,XY,+21 karyotype. Only 34 bone marrow cells were satisfactory for analysis, and all had a normal karyotype (Table 1). At 9 mo of age, he appeared to be healthy and developing normally. At the parents’ request, chromosome analyses of blood and bone marrow were not done.

### Table 1. Cytogenetic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tissue Sampled</th>
<th>Cells Counted</th>
<th>Percent of Cells Counted</th>
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</thead>
<tbody>
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<td>Age (days)</td>
<td>Blood</td>
<td>Marrow</td>
<td>Blood</td>
</tr>
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<td>50</td>
<td>22</td>
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</tr>
<tr>
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<td>70</td>
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<td>96</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>24</td>
<td>0</td>
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</table>

*Not applicable.

**DISCUSSION**

The transient leukemoid reaction or “transient acute leukemia” in patients with Down syndrome is a well recognized but poorly understood phenomenon. In a review of 56 newborns with Down syndrome who had the clinical and hematologic features of acute leukemia,2 the hematologic disorder resolved “spontaneously” in 21. Resolution also occurred in 4 children with Down syndrome who developed the leukemoid condition when they were 1 mo to 3 yr old. The mechanism of this transient leukemoid reaction is not understood, but it may indicate ineffective regulation of myelopoiesis due to delayed maturation of the myeloid and other bone marrow elements.2,3 Also, some of these children may have a physiologic stress produced by associated conditions, such as blood group incompatibility, infection, or heart disease, that may stimulate an overreaction of the myeloid elements in the bone marrow.

In the English literature there are nine case reports of cytogenetic studies in newborns with Down syndrome who had spontaneous resolution of a condition indistinguishable from acute leukemia.4-12 Six of these nine patients had a 47, + G karyotype and were still free of disease 1.5–4 yr later. Another died when he was 8 mo old and had no evidence of leukemia at autopsy. The last two patients developed leukemia again when they were about 2 yr old. At birth, one patient had a small percentage of bone marrow cells with an abnormal karyotype (48,XY,+21,+C).8 This clone disappeared spontaneously but reappeared when fulminant acute leukemia developed. The other was a 2-yr-old who had an abnormal clone (59, +4C, +3D, +E, +2F, +3G) at age 2 in addition to the trisomy 21 karyotype; cytogenetic studies were not done during the neonatal period.9 There is only one report of transient spontaneous remission of acute leukemia in a phenotypically normal newborn, and this patient had a normal karyotype.13

In our patient, all of the cells from blood samples incubated with PHA had the 47,XY,+21 karyotype, although only 70% were myeloblasts. This finding was puzzling, since the PHA should have stimulated the proliferation of thymus-derived lymphocytes, and some normal karyotypes should have been found. Similarly, trisomy 21 was present in all cells from the bone marrow when only 50% of it had been replaced by myeloblasts. The absence of normal karyotypes may indicate that the proliferation of trisomic cells suppressed production of the cytogenetically normal cells. Within 3 mo, this apparent proliferative advantage was lost. Cells with a normal karyotype became dominant, and myeloblasts disappeared from the blood. Also, none of the trisomic cells persisted in the marrow, although the percentage of marrow blasts was still slightly increased (9%).

In about half of the cases of acute myeloblastic leukemia, the malignant cells have an abnormal karyotype, and gain, loss, or rearrangement of chromosome 21 occurs with increased frequency.14 At first it was not clear whether the blood and marrow cells with trisomy 21 in our patient represented a malignant clone or his “normal” somatic cells. However, later studies of skin fibroblasts indicated that the child had mosaicism for trisomy 21. It is likely that this child had a leukemoid reaction involving the trisomic cells that subsequently were replaced by cells with a normal karyotype. Mosaicism for trisomy 21 may be the basis for the transient leukemoid reaction in some newborns. This may also apply to newborns who are phenotypically normal, as was the case for our patient.

Serial cytogenetic analysis should help to distinguish between congenital acute leukemia and transient leukemoid reactions in newborns. Further, any newborn suspected of having leukemia should have cytogenetic analysis of blood and bone marrow. Irrespective of the phenotype, findings of trisomy 21 should warrant chromosome analysis of skin fibroblasts to check for mosaicism. These patients should not be given chemotherapy unless their disease progresses despite supportive treatment. Patients with
a normal karyotype and those with abnormal karyotypes other than trisomy 21 probably should be treated, since the likelihood of spontaneous resolution is remote.\textsuperscript{13}

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REFERENCES

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