BRIEF REPORT

A Cytogenetic Study of Acute Erythroleukemia in Children

By Paul C. Dyment, John Melnyk and Charles A. Brubaker

The study of leukemia by cytogenetic techniques has been considerably productive in the past few years. The finding of the Philadelphia chromosome anomaly in chronic myelogenous leukemia by Nowell in 1960 has been confirmed by many others. Acute leukemia in children has been found to be characterized by marked hyperploidy of a variety of patterns not constant from patient to patient. Cytogenetic studies have been performed on adults with erythroleukemia (EL) by several authors, but their findings are inconstant, although when an abnormality was found it was usually characterized by varying degrees of hypoploidy.

The results of bone marrow chromosome analyses of four children with EL have been published. The first case was reported by McClure et al. to have a modal number of 45 chromosomes in direct and cultured marrow cells, and 46 chromosomes in cultured blood cells. They considered this to be an example of mosaicism. The missing chromosome in the bone marrow was one of the C group. The second case was noted by Weatherall and Walker to have a line of cells trisomic for one of the C group of chromosomes. They considered the extra chromosome to have been one of the number 6 pair. The other two cases were reported in the Polish literature and were found to have varying degrees of hypoploidy with no constant modal number. One of these children also demonstrated giant chromosomes.

Extensive further studies of EL have not been possible due to the rarity of the disease. At this hospital during the years 1962 to 1966 inclusive, there were 316 cases of leukemia in infants and children, of which 6 were diagnosed...
as EL. This is an incidence of approximately 2 per cent. This study is an investigation of 3 of these children with EL.

MATERIALS AND METHODS

During 1965 three children with EL were being cared for by this department and were available for study. Our concept of the disease entity we call erythroleukemia includes patients with pure erythroid neoplasia ("erythremic myelosis" or "DiGuglielmo's Disease") as well as those with an additional leukoblastic component. The diagnosis was made on these children after the fulfillment of most or all of the following criteria: 1) anemia; granulocytopenia; thrombocytopenia; presence of nucleated red cells, megaloblasts, or blast cells in the peripheral blood; 2) bone marrow examination showing crowding with megaloblastic erythroid elements and Auer bodies in granulocytic precursors. An increased number of myeloblasts was not considered essential for this diagnosis.

Chromosome Studies

Serial bone marrow aspirations were performed while the patients were in varying stages of their disease. The material thus obtained was studied for changes in chromosome number and morphology. The marrow aspirates were studied without prior culture using a modification of Reisman's "direct" method. Blood samples generally were obtained the same day as the bone marrow aspiration, and were cultured by a technic similar to that of Arakaki and Sparkes using phytohemagglutinin.

Patients

Case 1, a Caucasian boy, had the diagnosis of acute erythroleukemia made at this hospital in September, 1964, when 14 years of age. The patient required blood transfusions every 8 weeks. He received courses of treatment with antileukemia agents including prednisone, 6-mercaptopurine, methotrexate, and vincristine; however, his bone marrow and blood showed little or no response to these drugs. In November, 1965, his bone marrow converted to the pattern of acute granulocytic leukemia. He received cytosine arabinoside, an investigational antileukemia drug, for two months prior to his expiration in relapse in February, 1966.

Case 2, a Caucasian girl, had the diagnosis of acute erythroleukemia made at this hospital in October, 1964, when 11 years old. Remissions were not obtained with 6-mercaptopurine and prednisone in combination, nor with vincristine. She had a clinical remission of ten months' duration during therapy with methotrexate, and one of eight months' duration with cytosine arabinoside. She expired in relapse in September, 1966.

Case 3, a Caucasian boy, had the diagnosis of acute erythroleukemia made here in October, 1964, when 11 years of age. Partial clinical remissions were obtained with methotrexate, 6-mercaptopurine and prednisone in combination, and vincristine. He did not respond to cyclophosphamide. Monthly blood transfusions were required until cytosine arabinoside was commenced on August 30, 1965. His transfusion requirements then decreased, his clinical condition improved, and his bone marrow morphology became more normal. This response to cytosine arabinoside persisted for several months, but he expired in relapse in September, 1966.

RESULTS

The first two patients had normal karyotypes at all times. Patient No. 1 had two bone marrow and four blood specimens studied for chromosome number and morphology while in relapse over a 16 month period. Patient No. 2 had one bone marrow and blood study done while in relapse, and three bone marrow and two blood studies done while in remission, all taken during a 9 month period.

The summary of the findings on Patient No. 3 in six specimens of bone
<table>
<thead>
<tr>
<th>Date</th>
<th>Tissue</th>
<th>Chromosome Numbers</th>
<th>Treatment</th>
<th>Bone Marrow Morphology</th>
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<tbody>
<tr>
<td>5-24-65</td>
<td>1 Blood</td>
<td>0&lt;45 26(5) 1 0 33</td>
<td>6-MP</td>
<td></td>
</tr>
<tr>
<td>2 Marrow</td>
<td>2</td>
<td>45(8) 1</td>
<td></td>
<td>Relapse</td>
</tr>
<tr>
<td>7-16-65</td>
<td>3 Blood</td>
<td>20(7) 5(5) 0</td>
<td>6-MP</td>
<td></td>
</tr>
<tr>
<td>4 Marrow</td>
<td>4</td>
<td>24(4) 0</td>
<td>6-MP</td>
<td>Relapse</td>
</tr>
<tr>
<td>5-24-65</td>
<td>5 Blood</td>
<td>0 24(6) 1(1) 25</td>
<td>6-MP</td>
<td></td>
</tr>
<tr>
<td>8-30-65</td>
<td>6 Marrow</td>
<td>0 30(6) 3(3) 0</td>
<td></td>
<td>Relapse</td>
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<tr>
<td>8-17-65</td>
<td>7 Blood</td>
<td>2 20(7) 5(5) 0</td>
<td>6-MP</td>
<td></td>
</tr>
<tr>
<td>8-30-65</td>
<td>8 Blood</td>
<td>0 114(2) 0</td>
<td></td>
<td>CA.</td>
</tr>
<tr>
<td>9-20-65</td>
<td>9 Marrow</td>
<td>2(2) 11(2) 0</td>
<td></td>
<td>Partial remission</td>
</tr>
<tr>
<td>10 Marrow</td>
<td>10</td>
<td>0 14(3) 0</td>
<td></td>
<td>CA.</td>
</tr>
<tr>
<td>11-8-65</td>
<td>11 Blood</td>
<td>0 27(5) 0</td>
<td></td>
<td>Partial remission</td>
</tr>
<tr>
<td>11-15-65</td>
<td>12 Blood</td>
<td>0 25(4) 0</td>
<td></td>
<td>CA.</td>
</tr>
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<td>1-10-66</td>
<td>14 Marrow</td>
<td>0 7(2) 0</td>
<td></td>
<td>Partial remission</td>
</tr>
</tbody>
</table>

( ) = Karyotypes
6-MP = 6 mercaptopurine
CA. = Cytosine arabinoside

The chromosome numbers and bone marrow analyses of Patient 3 are given in Table 1. Blood and bone marrow analyses #1 and #2 showed a mode of 45 chromosomes. The karyotypes from cells with 45 chromosomes in both blood and bone marrow showed a chromosome to be missing from the C group (Fig. 1). The second analyses #3 and #4, of blood and bone marrow, showed an interesting situation. In the peripheral blood, 24 cells had a mode of 46 chromosomes and only one with 45 which was a broken cell. The chromosomes of the diploid cells were normal in distribution and morphology upon karyotyping. In the bone marrow specimen which was taken at the same time as the blood, mosaicism was found. Twenty cells were found to have 45 chromosomes, with one missing in the C group in all of the 7 cells which were karyotyped. The 5 cells with 46 chromosomes had a normal distribution. A similar dichotomy...
Fig. 1.—Karyotype no. 1 (blood) from patient no. 3, showing only 45 chromosomes with the loss of a chromosome from the C group.

was obtained the following month when the blood (#5) revealed a mode of 46 chromosomes while the marrow (#6) had a mode of 45 chromosomes with a missing C group chromosome.

Subsequent blood and bone marrow cultures showed 46 chromosomes of normal morphology and distribution in almost all of the cells analyzed. This change in modal number occurred following the institution of cytosine arabinoside therapy.

Chromosome studies from peripheral blood of both parents of Patient No. 3, his male sibling, and his maternal grandmother showed essentially normal karyotypes.

**DISCUSSION**

The cells which were analyzed probably represent two populations: one population from the phytohemagglutinin-stimulated lymphocytes which possibly represent the “normal” 46 chromosome cells, and another population of myeloproliferative cells which are at metaphase as they enter the circulatory system. This could explain the “dichotomy” and “mosaicism” evident in the studies on Patient No. 3.

Monosomy involving a chromosome from the C group has also been reported in a child with erythroleukemia by McClure et al. who also found a dichotomy between marrow and blood chromosome studies. Among the reported chromosome abnormalities in adults with EL, there have been three cases with aneuploidy of the C group alone. One showed a loss of a chromosome and the other two had an extra chromosome in the group. Two out of seven
children with EL (including the present cases) who have had their karyotypes reported have had a loss of a chromosome from the C group. Hence, aneuploidy of group C chromosomes has been found in a total of six cases of EL to date. This is of particular interest as Rowley et al. have recently described changes involving only the chromosomes in the C group in patients with myelodysplastic-myeoproliferative disorders. A more recent review has supported this finding that there is a preponderance of group C chromosomal abnormalities in the myeloproliferative syndromes. This might suggest that it is one of the C chromosomes which contains the genetic material essential for the maintenance of normal hematopoiesis.

SUMMARY

Three children with acute erythroleukemia were studied for chromosomal changes. Two of them had persistently normal karyotypes despite relapse. The third patient was missing a C chromosome, and had 45/46 mosaicism in the bone marrow and a dichotomy between blood (mode of 46) and bone marrow (mode of 45). All of these abnormalities were only evident when he was in relapse. Following partial remission induced with cytosine arabinoside, all subsequent analyses were normal. This is the third case reported of a child with erythroleukemia with aneuploidy in the C group of the chromosomes.

SUMMARIO IN INTERLINGUA

Tres juveniles con erythroleucemia acute esseva studiate relative a alterationes chromosonal. In duo, persistentemente normal karyotypos esseva constatate in despecto de recidivas. In le tertie patiente un chromosomes C esseva absente, e ille monstrava mosaicismo 45/46 in le medulla ossee e un dichotomia inter le sanguine (a modo de 46) e le medulla ossee (a modo de 45). Omne iste anormalitates esseva evidente solo quando le patiente esseva in recidiva. Post remission partial inducite per medio de arabinosido de cytosina, omne le sequentem analyses esseva normal. Isto es le tertie caso reportate de un juvenil con erythroleucemia a aneuploidia in le gruppo C del chromosomas.

ADDENDUM

Since submission of this manuscript, Castoldi et al. have reported 5 patients with EL with chromosomal changes involving groups G. and C. See Blood 31:202, 1968.

REFERENCES

7. Strosselli, E. and Bernardelli, E.: Il...


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