CONCISE REPORT

tdic(9;12): A Nonrandom Chromosome Abnormality in Childhood B-Cell Precursor Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study

By Andrew J. Carroll, Susana C. Raimondi, Dorothy L. Williams, Frederick G. Behm, Michael Borowitz, Robert P. Castleberry, Michael B. Harris, Richard B. Patterson, D. Jeanette Pullen, and William M. Crist

In a review of 432 children with newly diagnosed acute lymphoblastic leukemia (ALL), we identified a new nonrandom translocation, tdic(9;12)(p11;p12), in the leukemic marrow cells of eight patients. Seven had hypodiploid karyotypes that lacked chromosomes 9 and 12 and contained a der(12), tdic(9;12); the eighth had a pseudodiploid karyotype with two normal 9 chromosomes, one normal 12 and the der(12), tdic(9;12). Abnormalities involving chromosomes other than 9 and 12 were noted in four of the eight patients. All cells with the tdic(9;12) expressed both the common ALL antigen and HLA-DR. Cytoplasmic immunoglobulin, a marker of pre-B ALL, was detected in one case with the tdic(9;12) but was absent in the other seven. Our results suggest that the tdic(9;12)(p11;p12) rearrangement is specifically associated with leukemic B cell precursors.

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CHROMOSOMAL rearrangements have been identified as the single most important prognostic variable in childhood acute lymphoblastic leukemia (ALL). Moreover, certain nonrandom rearrangements, including the t(4;11) in infants with undifferentiated acute leukemia, the t(8;14) in B cell ALL, the t(1;19) in pre-B cell ALL, and the t(11;14) and t(10;14) in T cell ALL are associated with specific clinically and immunologically defined subclasses of ALL. Other chromosomal abnormalities often found in the blast cells of patients with ALL include the t(9;22), a deletion or rearrangement of 9p and of 12p. These structural abnormalities are usually found in pseudodiploid karyotypes and are seen less frequently in other ploidy groups. We have reviewed the cytogenetic features of 432 children with newly diagnosed ALL and have found a new nonrandom translocation, tdic(9;12)(p11;p12), in the leukemic B cell precursors of eight patients, seven of whom had hypodiploid karyotypes.

MATERIALS AND METHODS

Patients. A total of 432 consecutive cases of ALL with fully banded chromosomes were available for review. Their distribution according to referral center was: St Jude Children's Research Hospital, 187 cases studied between 1984 and 1986; University of Alabama at Birmingham (UAB), 100 cases studied between 1979 and 1985; and the Pediatric Oncology Group (POG) 8600 study, 145 cases in which marrow specimens were shipped to the UAB cytogenetics laboratory for chromosome analysis between January and June 1986. All patients were advised of the procedures and attendant risks, in accordance with institutional guidelines, and informed consent was obtained in each instance.

Immunologic characterization. After separation on a Ficoll-Hypaque gradient, the leukemic marrow cells were evaluated by standard techniques for surface immunoglobulins (slg), cytoplasmic immunoglobulins (clg), and receptors for sheep erythrocytes. In cases of pre-B or B cell ALL, >10% of the blasts expressed either clg or slg. A case was considered E-rosette positive if >40% of the blasts formed heat stable E-rosettes. Surface antigens, including CALLA (CD10), B1 (CD20), and HLA-DR, were determined by indirect immunofluorescence or, in some cases, by microcytotoxicity assays with use of heteroantisera, as previously described. In the cytotoxicity assays, 20% reactivity above control was considered positive in immunofluorescence.

Chromosome analysis. Bone marrow samples from the 187 patients studied at St Jude Hospital were processed directly according to the method of Williams et al. Samples from the 100 patients seen at UAB were either processed directly or placed in short-term culture, or both. Samples from the 145 POG patients were placed in RPMI 1640 supplemented with 15% fetal calf serum and shipped overnight to the UAB cytogenetics laboratory. On arrival, they were subjected to short-term (24 hour) culture. Routine methods were used for culture harvest, slide preparation, and GTG-banding. Karyotypic designations were assigned according to the International System for Human Cytogenetic Nomenclature.

RESULTS

Three hundred twenty-eight (76%) of the 432 cases studied had a cytogenetically abnormal clone, eight of which (Table 1) showed a translocation involving chromosomes 9 and 12. The resulting derivative chromosome appeared to be dicentric with breakpoints tentatively assigned at 9p11 and 12p12; consequently, the rearrangement was designated tdic(9;12)(p11;p12)(Fig 1). We are aware that, on close examination of the derivative chromosomes shown in Fig 1, it could be reasonably suggested that the chromosome breakpoints are slightly different in each of the three cases. While we cannot rule out case to case variation in breakpoints, it is also possible that the apparent differences are the result of contracted chromosomes since we observed a similar degree...
Table 1. Cytogenetic Findings in the Eight Cases With tdic(9;12)

<table>
<thead>
<tr>
<th>Case No</th>
<th>No. of Metaphases Examined</th>
<th>Abnormal Metaphases (%)</th>
<th>Abnormal Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>20</td>
<td>45,XY, -9, -12, +der(12),tdic(9;12) (p11;p12)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>45</td>
<td>45,XY, -9, -12, +der(12),tdic(9;12) (p11;p12)</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>90</td>
<td>45,XY, -9, -12, +der(12),tdic(9;12) (p11;p12)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>80</td>
<td>45,XY, -9, -12, +der(12),tdic(9;12) (p11;p12)</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>50</td>
<td>45,XY,del(X)(q26), -9, -12, +der(12),tdic(9;12)(p11;p12)</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>95</td>
<td>45,XY,del(7)(p15), -9, -12, +der(12),tdic(9;12)(p11;p12)</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>80</td>
<td>45,XX, -5, -9, -12, +der(12),tdic(9;12)(p11;p12), +mar(?14), ?dup(6)(q21q26)</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>75</td>
<td>46,XY, -12, +der(12),tdic(9;12) (p11;p12)(60%)/45,XY, -8, -9, -12 +der(8),t(8;9)(p23;q13), +der(12),tdic(9;12) (p11;p12)(15%)</td>
</tr>
</tbody>
</table>

of variation between metaphases from individual patient cultures. The fact that the alternate derivative chromosome, containing the remaining short-arm material from chromosomes 9 and 12, was absent in all eight cases supports our contention that the translocation results in a dicentric chromosome. Furthermore, C-banding demonstrated the presence of the 9qh region on the der(12) chromosome in each of the three cases examined in this manner. Seven cases were hypodiploid, lacking a 9 and a 12 chromosome, and contained a der(12),tdic(9;12). The eighth case had a pseudodiploid karyotype with two normal 9 chromosomes, one normal 12 and the der(12),tdic(9;12). Abnormalities involving chromosomes other than 9 and 12 were noted in four of the eight cases. One case had two cytogenetically abnormal clones, both with the tdic(9;12). The proportions of cytogenetically normal cells in each case ranged from 5% to 80%.

Table 2 lists the clinical and laboratory findings in the eight cases with the tdic(9;12). Blast cells uniformly expressed both CALLA and HLA-DR. In five of seven cases in which it was determined, blast cells also expressed CD20 (B1). In seven cases the blast cells were morphologically classified as FAB L1. Cytoplasmic Ig was detected in one case. With the possible exception of male predominance (M:F ratio, 7:1), there were no obvious variations in clinical features that would distinguish these patients from the larger group with B cell precursor ALL lacking the tdic(9;12). Leukocyte counts ranged from 2.9 to 132 × 10^9/L and ages from 3 to 16 years. Three patients had extramedullary disease at the time of the diagnosis.

DISCUSSION

These results suggest that a rearrangement involving the short arms of chromosomes 9 and 12, tdic(9;12)(p11;p12) is an acquired, nonrandom chromosome abnormality with a frequency of ~2% among children with ALL. It appears to be limited to cases of B cell precursor ALL, specifically those characterized by CALLA, HLA-DR, and usually CD20 expression, a phenotype seen in 25% to 30% of cases of ALL in children. It may occur much more frequently in boys, as has been noted for chromosome 9p abnormalities in ALL.6,7,9

We are aware of only two other reports of a similar 9:12 translocation. The LAZ 221 cell line, established from the peripheral blood of a patient with “null” cell ALL, was characterized as having a karyotype of 45,XX, -9, -12,
could be included in either or both of these cytogenetic abnormalities in I0% newly diagnosed cases. The short arm of chromosome 9 or the short arm of chromosome 12 seem to be included in reports describing 9p or 12p abnormalities. N Clear(9;12) may define a distinct subgroup of patients who share a similar immunophenotype. Moreover, the same abnormalities have been identified in a child whose blast cell karyotype was 45,XY,-9,-12, +der(12),t(9;12)(q1;p13). Further examination of this case indicated that the abnormality was the same as that in our eight cases (NA. Heerema, personal communication, January 1987).

Deletions or rearrangements involving the short arm of chromosome 9 or the short arm of chromosome 12 seem to be equally common among children with ALL, with each occurring in ~10% newly diagnosed cases. Thus, the t(9;12) may define a distinct subgroup of patients who could be included in either or both of these cytogenetic categories. In fact, cases no. 2, 5, and 6 were previously included in reports describing 9p or 12p abnormalities. In addition, cases no. 3 through 5 were included in a report concerning hypodiploidy and its association with treatment outcome in childhood ALL.

Many nonrandom chromosomal translocations associated with chronic or acute leukemia involve breakpoints at or near the assigned loci for genes encoding proteins that affect cell growth. In view of the fact that the c-Kirsten-ras gene has been mapped to 12p11.1-p12.1, molecular studies of cases with the t(9;12) appear warranted.

The clinical significance of the t(9;12) is uncertain since so few patients with the abnormality have been reported and the follow-up times for most of them are short. Nevertheless, all eight patients described in this report attained complete remission and remain free of leukemia for 5 to 36 months (median, 10 months). Previous reports indicating that the presence of a chromosomal translocation or hypodiploidy confers a poor prognosis suggest that patients with the t(9;12) are at increased risk for treatment failure; however, longer follow-up is required to substantiate this impression.

### Table 2. Clinical and Laboratory Findings for the Eight Cases With t(dic)(9;12)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>FAB Type</th>
<th>Age(yr)</th>
<th>Sex</th>
<th>WBC (x 10/L)</th>
<th>Hb (mg/dL)</th>
<th>Immunophenotype</th>
<th>CALLA</th>
<th>HLA-DR</th>
<th>B1</th>
<th>Extramedullary Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>3</td>
<td>M</td>
<td>2.9</td>
<td>4.1</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>16</td>
<td>M</td>
<td>6.1</td>
<td>12.3</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>15</td>
<td>M</td>
<td>19.0</td>
<td>11.2</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>L1</td>
<td>4</td>
<td>M</td>
<td>15.1</td>
<td>8.7</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>L1</td>
<td>4</td>
<td>M</td>
<td>122.0</td>
<td>4.4</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>L1</td>
<td>8</td>
<td>M</td>
<td>44.2</td>
<td>6.5</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>L2</td>
<td>6</td>
<td>F</td>
<td>8.2</td>
<td>5.8</td>
<td>Common</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>L1</td>
<td>12</td>
<td>M</td>
<td>3.7</td>
<td>9.2</td>
<td>Pre-B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: NT, not tested.

+ t(9q12q). In a review of 70 cases of ALL, Heerema et al identified a child whose blast cell karyotype was 45,XY,-9,-12, +der(12),t(9;12)(q1;p13). Further examination of this case indicated that the abnormality was the same as that in our eight cases (N.A. Heerema, personal communication, January 1987).

Deletions or rearrangements involving the short arm of chromosome 9 or the short arm of chromosome 12 seem to be equally common among children with ALL, with each occurring in ~10% newly diagnosed cases. Thus, the t(dic)(9;12) may define a distinct subgroup of patients who could be included in either or both of these cytogenetic categories. In fact, cases no. 2, 5, and 6 were previously included in reports describing 9p or 12p abnormalities. In addition, cases no. 3 through 5 were included in a report concerning hypodiploidy and its association with treatment outcome in childhood ALL.

### REFERENCES


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