Acute Lymphoblastic Leukemias With Deletion of 11q23 or a Novel Inversion (11)(p13q23) Lack MLL Gene Rearrangements and Have Favorable Clinical Features


Balanced translocations affecting the 11q23 region are among the most frequent chromosomal abnormalities in childhood acute lymphoblastic leukemia (ALL), comprising 5% to 6%. These cases consistently have a rearranged MLL gene and are associated with high-risk presenting features, hyperleukocytosis and younger age, and a poor treatment outcome. To assess the clinical and biologic significance of 11q23-associated structural chromosomal abnormalities other than translocations, we studied 17 cases of childhood ALL [14 with del(11)(q23) and 3 with inv(11)(p13q23)] that were identified among 785 cases with successful chromosome analysis. In contrast to reported cases with 11q23 and MLL gene rearrangement, our series was characterized by relatively low leukocyte counts (median, 15.1 x 10^9/L), expression of CD10 antigen but not myeloid-associated CD15 and CDw65 antigens, a relatively high frequency of T-cell immunophenotypes, and a generally favorable prognosis. All 13 cases with interpretable molecular analysis lacked MLL gene rearrangements. We suggest that most cases with deletions or inversions affecting the 11q23 region represent clinically and biologically different entities as compared with those defined by 11q23 translocation.

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Fig 1. Schematic representation of MLL gene. Locations of exons 1 through 21 are represented by black rectangles. BamHI, HindIII, EcoRI, and SacI restriction sites are denoted by B, H, E, and S, respectively. Regions of MLL identified by p98.40, ps4, 4.2E, and MLL probes are represented by dotted rectangles. The p98.40 probe detects a 15+-kb BamHI fragment (telomeric to exon 1 through exon 5). MLL and ps4 probes recognize an 8.5-kb BamHI fragment (exons 5 through 11). The 4.2E probe recognizes 8.5-kb (exons 5 through 11) and 15+ kb (exons 11 through 18) BamHI fragments. (Reproduced from The Journal of Clinical Investigation, 1994, volume 93, pp 429-437, by copyright permission of The American Society for Clinical Investigation.a Modified and reprinted with permission.a)

in the hybridization solution to block repetitive sequences. All blots include DNA with germline MLL genes and DNA from the RS4;11 cell line, which contains one germline and one rearranged MLL gene.11 Hybridized membranes were exposed to Kodak XAR-5 film (Eastman Kodak, Rochester, NY) at -70°C for 5 to 7 days.

Fig 2. Representative G-banded partial karyotypes from patients with a newly recognized inversion (11)(p13q23): (A) patient no. 15, (B) patient no. 16, (C) patient no. 17.

RESULTS

Of the 14 cases with a del(11)(q23), the deletion was the only chromosomal abnormality in 7 (nos. 1 through 7); the remainder had additional changes (Table 1), including a t(9;22)(q34;q11) in 2 and a 12p abnormality in 3. The modal number was 46 in all but 3 cases (1 with 45 and 2 with 47 chromosomes). In none of these 14 cases was there cytogenetic evidence of an 11q23 translocation or an interstitial deletion. Although the variability in the breakpoint assignment within this region cannot be defined further with any degree of certainty, 2 cases (no. 3 and 8) might have a more proximal breakpoint at 11q22-23.

The median age of the 8 boys and 6 girls with a del(11)(q23) was 7.5 years at diagnosis (range, 2.3 to 14.7 years). Initial leukocyte counts ranged from 1.2 to 85.7 × 10^9/L (median, 7.5 × 10^9/L). Of the 13 del(11)(q23) cases with complete immunophenotyping, 8 were classified as early pre-B, 2 as pre-B, and 3 as T-cell ALL. CD10 was expressed in all but 2 cases with T-cell ALL. CD15 and CDw65 were expressed in the T-cell case. The infant with T-cell ALL had a hematologic relapse and has...
Table 1. Summary of Clinical and Laboratory Data for Patients With a del(11q23) or inv(11)(p13q23)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Race</th>
<th>Leukocyte Count (x10⁹/L)</th>
<th>Karyotype</th>
<th>MLL Status</th>
<th>Immunophenotype</th>
<th>CD10</th>
<th>CD15</th>
<th>CDw65</th>
<th>Remission Duration (mo)</th>
<th>Type of Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.9/W</td>
<td>6.4</td>
<td></td>
<td>46,XY,del(11)(q23)(6);46,XY;14</td>
<td>ND</td>
<td>Early pre B</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>149+</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>12.9/W</td>
<td>11.4</td>
<td></td>
<td>46,XY,del(11)(q23)(8);46,XY;12*</td>
<td>ND</td>
<td>T</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>37</td>
<td>Kidney</td>
</tr>
<tr>
<td>3</td>
<td>2.9/W</td>
<td>3.8</td>
<td></td>
<td>46,XY,del(11)(q23)(8);46,XY;13*</td>
<td>G</td>
<td>Early pre B</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>90+</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>4.7/W</td>
<td>6</td>
<td></td>
<td>46,XX,del(11)(q23)(9);46,XX;16*</td>
<td>G</td>
<td>Pre B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30+</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>14.4/W</td>
<td>52</td>
<td></td>
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<td>G</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>27+</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>14/W</td>
<td>18.9</td>
<td></td>
<td>46,XY,del(11)(q23)(7);46,XY;10*</td>
<td>G</td>
<td>Early pre R</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>20</td>
<td>CNS</td>
</tr>
<tr>
<td>7</td>
<td>11.9/W</td>
<td>76.7</td>
<td></td>
<td>46,XY,del(11)(q23)(2);46,XY;29*</td>
<td>G</td>
<td>T</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>18+</td>
<td>—</td>
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<tr>
<td>8</td>
<td>14.7/W</td>
<td>85.7</td>
<td></td>
<td>45,XX,inv(5)(p13q14);del(10)</td>
<td>G</td>
<td>T</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>0</td>
<td>IF</td>
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<tr>
<td>9</td>
<td>13.3/W</td>
<td>7.5</td>
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<td>46,XY,inv(5)(q23)(q22-23),dic(12;17)(p11;p11)(12;46,XX;8)*</td>
<td>ND</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>54+</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>7.5/W</td>
<td>3.5</td>
<td></td>
<td>46,XX,t(9;22)(q34;q11);del(11)(q23);[5]/47,XY,del(11)(q23),+18[5]/46,XY;2*</td>
<td>G</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>43+</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>6.1/B</td>
<td>15.1</td>
<td></td>
<td>47,XX,t(11)(p22);p22,t(13);t(12);q21;13),t(12);q23;[7]/46,XX;13</td>
<td>G</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>38+</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>6.2/W</td>
<td>43.4</td>
<td></td>
<td>45,XY<a href="7">t(11;11)(q23)</a>/46,XX;10</td>
<td>G</td>
<td>Pre B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30+</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>9.2/W</td>
<td>2.4</td>
<td></td>
<td>46,XX,inv(11)(p13q23)</td>
<td>G</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>16+</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>6.8/W</td>
<td>1.2</td>
<td></td>
<td>46,XX,inv(11)(q23)(22-23),del(12)(p12),der(11)(t;21);q21;13;q22(15)/46,XX;10</td>
<td>G</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>9+</td>
<td>—</td>
</tr>
<tr>
<td>Inversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.5/W</td>
<td>17.7</td>
<td></td>
<td>46,XY,inv(11)(p13q23)[25]*</td>
<td>G</td>
<td>T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>8</td>
<td>H</td>
</tr>
<tr>
<td>16</td>
<td>2/W</td>
<td>21.9</td>
<td></td>
<td>46,XX,inv(11)(p13q23)[25],10</td>
<td>ND</td>
<td>Early pre B</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>102+</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>2/W</td>
<td>71.4</td>
<td></td>
<td>46,XX,inv(11)(p13q23)[12]/47,XX,del(11)(q23)[12]/47,XX,del(11)(q23)[12]*</td>
<td>G</td>
<td>Early pre B</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>7+</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: G, germline; ND, not done; NA, inadequate sample for markers; W, White; B, Black; kidney, kidney relapse; CNS, CNS relapse; IF, induction failure; H, hematologic relapse.

* Karyotype previously reported.

died, whereas the 2 other children remain in remission for 7+ and 102+ months.

DNA was available for Southern blot hybridization for 11 of 14 cases with del(11) and 2 of 3 cases with inv(11). All 13 cases lacked evidence of a rearranged MLL gene using the cDNA MLL probe with BamHI, HindIII, and Sac I digests (Fig 3). To further exclude an MLL break outside of the region detected by the 0.74-kb MLL probe, membranes with BamHI- or HindIII-digested DNA were stripped and reprobed with 4.2E, p98.40, and ps4. Studies with these three probes likewise showed only germline MLL bands. Slight differences in the amounts of loaded DNA for each patient sample precluded qualitative assessment of the number of MLL copies detected by Southern blot. Densitometric Southern blotting using other 2 copy genes as baseline controls was not performed to search for evidence of deletions of an MLL locus.

DISCUSSION

The clinical characteristics of the 14 patients with a del(11)(q23) and the 3 with an inv(11)(p13q23) differed from those of patients with 11q23 translocations. The leukemic cell burden was relatively small; only 4 cases had an initial leukocyte count greater than 50 x 10⁹/L and 1 each had CNS involvement or splenomegaly. Moreover, expression of the myeloid-associated CD15 and CDw65 antigens was limited to single cases with a deletion or inversion. T-cell ALL, which is unusual among cases with 11q23 translocations and structural abnormalities affecting the 11q23 region do not appear to confer a poor prognosis unless there is molecular evidence of MLL rearrangement.
Previous molecular studies of cases with a deletion or inversion of the 11q23 region have yielded discrepant results regarding breaks in an MLL locus. Rearrangements of MLL with BamHI digests and probes as used in our cases were reported in 2 infants with M4 and M5 AML and a del(11)(q23) and del(11)(q21), respectively; in 2 cases of acute leukemia with an interstitial deletion of 11q12 in an infant and a 5-year-old child with a del(11)(q23); in an adult with secondary AML and a del(11)(q23.3-q24); in an infant with ALL and del(11)(q23); and in a de novo ALL patient with a del(11)(q23). By contrast, MLL rearrangements were not found in 3 leukemias and 17 lymphomas with other 11q23 abnormalities that included deletions and duplications of 11q23 in one study,4; 2 infants with an 11q23 cytogenetic alteration,13 2 adults with therapy-related AML and a del(11)(q13q23) or del(11)(q14q23),35 and an inv(11)(p11q23) in a case of Philadelphia-positive chronic myelogenous leukemia.36 Although it is difficult to reconcile the apparent higher frequency of involvement of MLL in patients in the literature, in some instances these cases may represent undetected translocations. This was demonstrated by Yamamoto et al36 in a cell line with a del(11)(q23) using conventional cytogenetic analysis, but determined to have an MLL-LTG19 transcript using reverse transcription-polymerase chain reaction. Likewise, Kobayashi et al.,38 using fluorescence in situ hybridization, have shown that 11q23 deletions are mostly caused by undetected translocations.

The molecular probes (MLL, p98.40, ps4, and 4.2E) used in this study are sufficient to detect all described breaks between exons 2 and 18 of MLL.4,9,29,30 This study does not exclude the possibility of breaks proximal and distal to exons 2 and 18, respectively. It is also possible that the entire MLL locus is lost or that a locus other than MLL is involved in the cases with chromosome 11q23 deletions. Similarly, genes other than MLL within band q23 may be rearranged in the cases with inversions of chromosome 11. Fluorescence in situ hybridization studies with probes to distal and proximal regions of MLL will help in further delineating where the breaks are occurring in these cases.

Infants with ALL and rearrangements of MLL have a poor clinical outcome.9,10,12,13 The frequency of MLL gene involvement and its effect on prognosis in older children with 11q23 translocations or other 11q23 abnormalities is uncertain. Recent studies have suggested that such rearrangements occur not only in association with the common 11q23 translocations but in other 11q23 abnormalities as well.5,11,29,32,33 By contrast, we found that childhood ALL with the deletion of 11q23 or a novel inversion (11)(p13q23) lacked MLL gene rearrangement. Furthermore, patients with B-lineage ALL and del(11)(q23) or inv(11)(p13q23) with no molecular evidence of MLL gene rearrangements do not appear to share the unfavorable prognosis of 11q23 translocations that involve MLL.

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REFERENCES


Fig 3. Southern blot of BamHI-digested DNA of leukemic marrow cells from patients with del(11)(q23) or inv(11)(p13q23). Lanes labeled "N" and "RS" contain DNA from cell lines with normal 11q23 and t(4;11)(q21;q23), respectively. Other lanes are labeled with the case number according to Table 1. Blots were hybridized with a cDNA probe (MLL) that recognizes sequences between exons 5 and 11 of the MLL gene. The 8.5-kb germline band from normal MLL is indicated by the arrowhead. None of the patient samples shows a rearranged MLL gene. The faint extra band in lane 4 is due to partial digestion of DNA.


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arrangement exhibits B lineage and monocytic characteristics. Blood 65:21, 1985


Acute lymphoblastic leukemias with deletion of 11q23 or a novel inversion (11)(p13q23) lack MLL gene rearrangements and have favorable clinical features

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