The t(1;22)(p13;q13) Is Nonrandom and Restricted to Infants With Acute Megakaryoblastic Leukemia: A Pediatric Oncology Group Study


We report the nonrandom occurrence and frequency of the t(1;22)(p13;q13) in acute myeloid leukemia (AML) and its close association with the French-American-British M7 subtype of AML in infants (<1 year). This chromosomal abnormality occurred in 6 of 252 (2.4%) children and adolescents with AML (6 of 28 infants, 22%; 6 of 18 M7 AML cases overall, 33%; and 6 of 6 M7 cases in infants). Infants with AML of M7 subtype and the t(1;22) often presented with prominent abdominal masses. Two of these infants were not treated and died early. Three of four treated infants entered complete remission with therapy for AML; the remaining infant died of hemorrhage on day 8. Of the three infants who entered remission, only one remains alive and disease free at 5+ months. The other two infants relapsed in the bone marrow at 5 and 2 months from the start of therapy, respectively. We conclude that M7 AML with the t(1;22) usually presents in infants with extensive infiltration of abdominal organs by leukemic cells and may confer a poor prognosis despite intensive AML-directed treatment. Identification of this nonrandom translocation exclusively in infants with acute megakaryoblastic leukemia (AMKL) implies that it may serve as an additional diagnostic marker for this disease and links it to the pathogenesis of AMKL in infants.

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ACUTE MYELOID leukemia (AML) comprises approximately 15% of newly diagnosed cases of acute leukemia in children. Until recently, AML was believed to be distributed among six morphologically distinct subtypes (designated M1 through M6 as defined by the French-American-British [FAB] Cooperative Group).1 Although a seventh morphologic subtype, derived from megakaryoblasts, has been recognized for over 10 years, reliable cytochemical and morphologic criteria to distinguish M7 AML from acute lymphoblastic leukemia (L2) or undifferentiated AML (M0) were lacking.2 More recently, immunologic studies using monoclonal antibodies (MoAbs) that recognize platelet-associated membrane antigens have facilitated specific identification of megakaryocyte precursors.3 With increased availability of these newer techniques, the reported frequency of acute megakaryoblastic leukemia (AMKL) has increased.4 Recent reports indicate that this subtype comprises 8% to 10% of acute leukemias in adults5,6 and about 3% of pediatric AML.7 Various studies have shown that AMKL is frequently accompanied by myelofibrosis in both children and adults and is seen with abnormally high frequency in children with Down’s syndrome.8 No acquired recurring cytogenetic abnormality has yet been reported in this relatively rare subtype of acute leukemia. We identified a specific translocation, t(1;22)(p13;q13), in six infants with AMKL. This cytogenetic abnormality was specific to infants with the AMKL subtype in studies of 252 children with AML accrued to the Pediatric Oncology Group (POG) over a 24-month period (ending in May 1990). No cases of the t(1;22)(p13;q13) were identified in concurrent POG studies of childhood acute lymphoblastic leukemia (n = 2,382). We report here the clinical and biologic features and response to therapy of infants with AMKL and the t(1;22).

MATERIALS AND METHODS

Patients. Between June 1988 and May 1990, 252 children, 28 of whom were infants, with newly diagnosed AML (18 with AMKL) and 2,382 with ALL (from February 1986) were accrued to POG institutions. All patients with a diagnosis of AML were eligible, but it is possible that some infants with Down’s syndrome were not entered because of parental or investigator discretion. Diagnoses were made according to FAB criteria in all cases except 4 and 6 (diagnosed by biopsy of choroma or hepatic tissues). Routine cytochemistry studies, including myeloperoxidase or Sudan black B and esterase stains (Naphthol-ASD-acetate [NASDA], alpha-naphthyl-acetate [ANA], and alpha-naphthyl-butyrate [ANB]) were performed at POG member institutions and repeated in a central reference laboratory. Samples of bone marrow and/or blood were collected before therapy began for immunologic marker analysis and cytogenetic characterization. Written informed consent was obtained from patients, parents, or guardians in accordance with institutional guidelines. The three male and three female infants with the t(1;22) ranged in age from 10 days to 10 months (see Table 1). Four patients were white, one was black, and one was Hispanic.
Four of the six infants with the t(1;22) were treated on the POG 8821 study for children with AML (unpublished POG frontline AML protocol); the two other infants were not treated because of parent refusal or early death. The therapy was intensive and comprised initial daunorubicin, cytarabine, and 6-thioguanine for induction of remission followed by alternating cycles of etoposide and 5-azacytidine, high-dose cytarabine and daunorubicin, and repeated induction therapy.

**Immunologic characterization.** Blast cells from patients enrolled in these studies were sent to the POG central reference laboratories for flow cytometric analysis using MoAbs that recognize B-lymphoid antigens (CD19, CD20, CD22), T-lymphoid antigens (CD7, CD5, CD2, CD3, CD4, CD8), the common ALL antigen (CD10), the transferrin receptor (CD71), the natural killer cell-associated antigen (CD56), monomyeloid-associated antigens (CD33, CD13, CD15, CD11b, CD14), the progenitor-cell-associated antigen (CD34), and HLA-DR. For five of the six patients described below and all patients with AML, studies were also conducted using antibodies specific for the platelet-associated antigens CD61 (GPIIIa), CD41a (GPIIb/IIIa), and CD42b (GPIb). Cell surface antigens were arbitrarily considered as significantly expressed if \( \geq 30\% \) of the leukemic blast cells expressed the antigen. Blast cells from patient 6 were assayed for factor VIII antigen by the immunoperoxidase technique on liver tissue infiltrated by blast cells. For some cases, the quantity of leukemic cells available was insufficient to perform the full panel of antibody tests.

**Diagnostic criteria for AMkL.** We based the diagnosis of AMkL on the following criteria: (1) bone marrow morphology suggestive of megakaryoblasts, with cytoplasmic blebs, binucleation of blasts, cytoplasmic basophilia, and blast cell clumping, or of undifferentiated (FAB M0 or L2) subtype; (2) myeloperoxidase or Sudan black B expression by \( \geq 3\% \) of the leukemic cells; (3) expression on less than \( 30\% \) of cells of the B- or T-lymphoid markers CD10, CD19 (CALLA), CD19 (B4), and CD7 or CD5; and (4) expression on at least \( 30\% \) of leukemic blasts of at least one platelet-associated marker (factor VIII-related antigen, or CD41a, CD42b, CD61). Immunoperoxidase staining of leukemic blast cells in liver tissue for factor VIII antigen was used in patient 6 only.

**Chromosome analysis.** Bone marrow specimens for analysis in the POG cytogenetic reference laboratory were placed in sterile tubes containing RPMI 1640 supplemented with fetal calf serum and shipped overnight. On arrival, cells were placed in fresh medium and subjected to 24-hour culture. Specimens from several patients (including four of those described here) were submitted to cytogenetic laboratories at member institutions only for 24- and/or 48-hour culture. In all cases, routine methods were used for culture harvest, slide preparation, and G-banding. Chromosomes were identified and assigned according to the International System for Human Cytogenetic Nomenclature. All karyotypes, including the four not performed in the reference laboratory, were reviewed centrally.

### RESULTS

The t(1;22)(p13;q13) was identified in leukemic blast cells from 6 of 252 newly diagnosed children with AML. This translocation was not found in any of the patients with ALL studied. All six patients with the t(1;22) were infants (<12 months) and all had AMkL. Of 22 other infants with AML without the t(1;22) who entered this study, none had AMkL. The 12 other older children diagnosed with AMkL had no recurring chromosomal abnormality.

Five of six cases had enlarged livers and/or spleens. In three of four cases where liver and/or spleen size were measured, the span from below the mid clavicular line to the inferior organ edge was 4 to 7 cm (Table 1). Marked lymphadenopathy was observed in one infant (case 4), and ascites in another (case 6). None of these patients had central nervous system or testicular leukemia. Patient 4 presented with marked hepatosplenomegaly and lymphadenopathy and a mass in the region of the porta hepatitis containing leukemic cells which stained positively with anti-GPIIIa antibody; patient 6 was ultimately diagnosed by biopsy of the liver that showed extensive infiltration with leukemic blasts. The patients' white blood cell (WBC) counts ranged from 10 to \( 52 \times 10^9/L \) (median, \( 20 \times 10^9/L \)), hemoglobin levels from 5 to 16 g/dL (median, 7 g/dL), and platelet counts from 8 to \( 140 \times 10^9/L \) (median, \( 52 \times 10^9/L \)). The diagnosis of AMkL was nearly certain from morphologic findings (ie, cytoplasmic blebs, blast clumping, cytoplasmic basophilia) in two of these cases (patients 1 and 6), whereas the four other cases had more undifferentiated morphology with some suggestion of megakaryoblastic differentiation (ie, less prominent features as noted above).

No dysplastic features were noted in the myeloid or erythroid series. Bone marrow biopsies with reticulin stains from two infants (patients 3 and 4) showed myelofibrosis.

Selected results of immunologic marker studies are shown in Table 2. Blast cells from all six cases expressed at least one platelet-associated antigen. All cases were myeloperoxidase- and/or Sudan black B-negative, although three of five tested expressed the myeloid-associated antigen CD33 (Table 2). Expression of lymphoid-associated anti-

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**Table 1. Clinical and Laboratory Findings in Six Infants With AMkL.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (mo)</th>
<th>Sex</th>
<th>Liver Enlargement (cm)</th>
<th>Spleen Enlargement (cm)</th>
<th>Lymph Nodes</th>
<th>Hemoglobin (g/dL)</th>
<th>WBC (&gt;10⁹/L)</th>
<th>Platelets (&gt;10⁹/L)</th>
<th>Marrow Blasts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.2</td>
<td>10</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>F</td>
<td>4</td>
<td>5</td>
<td>-</td>
<td>7</td>
<td>21</td>
<td>140</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>6</td>
<td>11</td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td>4*</td>
<td>10</td>
<td>F</td>
<td>4</td>
<td>+</td>
<td>Marked ♠</td>
<td>7</td>
<td>18</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>M</td>
<td>6</td>
<td>7</td>
<td>-</td>
<td>16</td>
<td>52</td>
<td>81</td>
<td>35</td>
</tr>
<tr>
<td>6†</td>
<td>1</td>
<td>F</td>
<td>Ascites</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>21</td>
<td>41</td>
<td>7</td>
</tr>
</tbody>
</table>

*Had abdominal chloasma involving porta hepatitis and head of pancreas.

†Case diagnosed based on morphologic criteria (typical of M7) and demonstration of factor VIII antigen (immunoperoxidase technique) on leukemic cells from hepatic tissue.

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Table 2. Results of Immunologic Marker Studies of Six Infants With AMkL and the t(1;22)

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD42b* (GPIb)</th>
<th>CD41a (GPIb/IIa)</th>
<th>CD61 (GPIIIa)</th>
<th>Factor VIII Antigen (MY9)</th>
<th>CD33 (MY10)</th>
<th>CD34</th>
<th>CD19</th>
<th>HLA-DR</th>
<th>CD7 (Pan T)</th>
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<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>93</td>
<td>ND</td>
<td>ND</td>
<td>53</td>
<td>2</td>
<td>0</td>
<td>42</td>
<td>7</td>
</tr>
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<td>2</td>
<td>53</td>
<td>ND</td>
<td>58</td>
<td>+</td>
<td>17</td>
<td>38</td>
<td>16</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>ND</td>
<td>65</td>
<td>+</td>
<td>40</td>
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<td>ND</td>
<td>37</td>
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<td>9</td>
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<tr>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.

*Expressed as percent positive blasts. Antigen expression considered significant if expressed on 30% or more of the blast cells.

gens and common ALL antigen (CALLA; CD10) was absent in the five cases tested. Also, the blast cells from five of five cases tested failed to express the transferrin receptor or natural killer cell antigen. Two of five cases (cases 2 and 5) tested showed expression of CD34 (MY10), and HLA-DR was expressed in two other cases (cases 1 and 3). Approximately 15% of non-M7 AMLs also tested positive (ie, the antigen, CD61, CD41a, or CD42b, was expressed on 44% to 89% of the blasts), but all of these cases were myeloperoxidase- or Sudan black B-positive and had typical morphology of a non-M7 subtype of AML. None of 45 cases of ALL (T-cell, n = 6; B-progenitor cell, n = 39) expressed CD61, CD41a, or CD42b.

Karyotypes of these six patients are given in Table 3. Leukemic blast cells from patients 2, 3, 5, and 6 contained a pseudodiploid clone with a balanced 1;22 translocation as the only cytogenetic abnormality. The abnormal clones in patients 1 and 4 were hyperdiploid. Breakpoints appeared to be in the distal portion of band p13 on chromosome 1 and band q13 on chromosome 22 in metaphases from all six patients (Fig 1).

Two of these infants received no therapy. The parents of patient 5, who also had cystic fibrosis, refused consent for treatment and the infant died several months later. Patient 6 died of renal failure, acidosis, and other complications before therapy could be started. Three of the four infants who were treated achieved complete remission (patients 1, 2, and 3).

Table 3. Cytogenetic Findings in Six Infants With AMkL and t(1;22)(p13;q13)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Metaphases Examined (no.)</th>
<th>Abnormal Metaphases (%)</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>30</td>
<td>58,XY,+6,+6,+7,+8,+14,+17,+18,+19,+19,+21,+21,t(1;22)(p13;q13),+der(1)h(1;22)(p13;q13)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>55</td>
<td>46,XX,t(1;22)(p13;q13)</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>100</td>
<td>46,XX,t(1;22)(p13;q13)</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>71</td>
<td>54,XX,+2,+6,+7,+10,+15,+18,+19,−21,t(1;22)(p13;q13),+der(1)h(1;22)(p13;q13)</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>55</td>
<td>46,XY,t(1;22)(p13;q13)</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>22</td>
<td>46,XX,t(1;22)(p13;q13)</td>
</tr>
</tbody>
</table>

Fig 1. The t(1;22)(p13;q13) associated with AMkL in infants. (A) Diagram showing the G-banded pattern of the derivative (der) chromosomes and normal homologues. The arrows indicate the approximate positions of the breakpoints. (B) Representative partial karyotypes from patients 1, 2, 4, and 6.
3, and 4); patient 2 died of hemorrhage on day 8 of remission-induction therapy. The disease relapsed in the bone marrow at 5 and 2 months later in patients 1 and 4, respectively. Patient 3 remains in complete remission for 5+ months.

**DISCUSSION**

The most important finding in this study was that a chromosomal translocation, t(1;22)(p13;q13), was specific for megakaryoblastic leukemia in infants. Six of 252 patients with AML, all younger than 1 year at diagnosis and all with megakaryoblastic leukemia, had this translocation detected, in contrast to none in any other morphologic subtype of AML or ALL studied during the same time period. Overall, this translocation was identified in about one third of cases of AMkL, one fifth of cases of infant AML, and all cases of infant AMkL. However, we acknowledge that no infants with AMKL and Down's syndrome were entered in this study, indicating that investigators may be reluctant to enter such patients on very intense protocols, and suggesting that all infants with AMKL may not have been entered on study. Indeed, Koller et al11 observed the t(1;22) in only one of three infants with AMKL with cytogenetic studies demonstrating a clonal abnormality. The pattern of antigen expression in our cases and those from other reports is variable, but several reports suggest that the cell of origin in AMkL may be a multipotent hematopoietic stem cell. This suggestion is based primarily on the coexpression of megakaryocytic, myeloid, and/or lymphoid antigens with or without rearrangements of Ig or T-cell receptor genes in some cases of AMKL in both adults and children.11,12 Most infants with AMKL and the t(1;22) in this study presented with extensive infiltration of abdominal organs by leukemic cells, a feature not emphasized in the few similar previously reported infants or in older children or adults with AMKL. Myelofibrosis was a frequent finding in infants and children with AMKL with or without the t(1;22) and is frequently observed in adults with AMKL. Taken together, our findings suggest that the t(1;22) is specific for AMKL, occurs primarily or exclusively in infants, and may represent a clinically aggressive phenotype.

We used both positive and negative criteria for the diagnosis of AMKL because we and others have found that no single test is diagnostic. Platelet peroxidase is often present in erythroid leukemias13 and a case of myeloperoxidase-positive AMKL has been reported.14 Approximately 15% of non-M7 cases of AML in our study appeared to express platelet-associated antigens, although these cases had blasts that expressed myeloperoxidase or Sudan black B and most had FAB morphologic criteria indicating non-M7 differentiation (data not shown). These “false positive” cases may be due to platelets or platelet fragments sticking to the surface of blast cells. Bloomfield and Brunning15 have suggested that a panel of immunologic markers sufficient to rule out lymphoid origin be included in the work-up of undifferentiated acute leukemias, because AMKL cases may resemble ALL with L2 morphology. Five of five cases of AMKL with the t(1;22) tested had blasts that failed to express myeloperoxidase or Sudan black B, were megakaryoblastic or undifferentiated in appearance, expressed at least one platelet-associated antigen, and failed to express surface antigens (ie, CD10, CD19, CD7, or CD5) that are present on 95% or more of B- or T-lymphoid leukemias.15,16

We believe that the minimum diagnostic criteria for AMKL in children should include morphologic findings compatible with the diagnosis, absence of myeloperoxidase or Sudan black B staining of leukemic cells, and presence of one or more platelet-associated antigens (or platelet peroxidase) in the absence of B- or T-lymphoid antigens on the leukemic cells. Esterase stains may help suggest the diagnosis but are not specific.5,17 If these tests are applied uniformly in a prospective manner to the study of all cases of undifferentiated acute leukemia, a clearer clinical picture of AMKL should emerge.

A recent review of this diagnostic subtype noted that losses of chromosome 7 or 5 were frequent, as was gain of chromosome 8, either alone or in combination with other cytogenetic changes.18 Also, single cases with inv(16) (p13q22), del(20)(q11), and der(7)t(7;17)(p14;q22) were described as well as cases of chronic myeloid leukemia with the t(9;22) in megakaryoblastic crisis. Previously, Cairney et al19 noted random cytogenetic abnormalities and a single case with a t(11;22) and additional cytogenetic abnormalities. We are aware of five previous reported cases of infants with acute leukemia with a t(1;22) similar to the present cases (ie, with similar breakpoints).12,20-22 Four of these infants had AMKL11,21,22, the other case was classified as M620 but was diagnosed several years before designation of the M7 subtype by the FAB Cooperative Group.2 Breakpoints at bands 1p13 or 22q13 have rarely been reported in other types of neoplasia, suggesting that gene(s) critical to development of AMKL in a subset of infants are located at these breakpoints and targeting these chromosomal regions for molecular genetic studies. Band 1p13 involvement has been reported in a case of congenital FAB L2 lymphoid leukemia.23 This finding, considered together with the finding of frequent gain of the derivative chromosome 1 in hyperdiploid clones (cases 1 and 4), indicates a possible role of the der(1) junction in this subtype of leukemia.

Because the distinction of AMKL is not possible based on morphologic or cytochemical findings alone, and many centers have not had ultrastructural cytochemistry or specific immunologic markers readily available, it is likely that cases of AMKL have been diagnosed as ALL or non-M7 AML subtypes. Patients with AMKL treated with lymphoid-directed therapy have done poorly, but myeloid-directed protocols seem to produce remission rates equivalent to those seen in other patients with AML.4 The durability of these remissions remains to be established. Unfortunately, three of the four patients who were treated in our series failed to enter remission or have already relapsed, despite intensive chemotherapy for AML. Only one infant remains in continuous remission with limited follow-up (5+ months). Our patient series is too small to permit firm conclusions regarding the prognosis of infants with AMKL with the

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t(1;22). Nevertheless, long-term survivors of AMkL have been reported and intensive myeloid-directed therapy is recommended.}

Our findings of a strong association between the t(1;22)(p13;q13) and AMkL in infants suggests that prenatal genetic factors are involved in leukemogenesis in this form of AML. As with other nonrandom translocations, the strong association of infant AMkL with the p13 and q13 breakpoints on chromosomes 1 and 22, respectively, suggests that alterations in genes (e.g., N-ras, PDGF-β) at or near these sites participate in malignant transformation and proliferation of megakaryoblasts. Because PDGF-β stimulates fibroblast proliferation, it is tempting to hypothesize that activation of this gene due to chromosomal translocation or another mechanism accounts for the frequent myelofibrosis observed in AMkL. This possibility is testable.

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REFERENCES

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