

## CONCISE REPORT

# Pre-B Cell Leukemia Associated With Chromosome Translocation 1;19

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Chromosome banding studies on 60 children with acute lymphocytic leukemia (ALL), including "null," pre-B, B, and T cell phenotypes, were performed. In 4 of 17 patients with pre-B cell ALL, we noted a previously undescribed chromosome translocation, t(1;19)(q23;q13). This translocation

was not found in patients with "null" cell, B cell, or T cell ALL. Since each patient with the 1;19 translocation experienced early treatment failure, t(1;19)(q23;q13) may mark a subgroup of patients with pre-B cell ALL who have an especially poor prognosis.

**I**N 1978, a newly recognized type of acute leukemia, pre-B cell acute lymphocytic leukemia (ALL), was described.<sup>1</sup> Recently, a remarkable difference in response to treatment has been noted between children with pre-B cell versus "null" (non-B, non-T, non-pre-B) cell ALL.<sup>2</sup> The biologic basis for the relatively poor response to treatment of children with pre-B cell ALL is unclear. Both pre-B and "null" phenotypes of ALL present with similar clinical features, and both have the rearrangements of heavy chain genes, and occasionally of light chain genes, that characterize B cell progenitors.<sup>2,3</sup> The pre-B lymphoblasts are distinguishable only by the presence of cytoplasmic  $\mu$  chain (cIg) expression.

Cytogenetic abnormalities, including hypodiploidy or pseudodiploidy or the presence of a 4;11 translocation have recently been reported to predict a poor response to treatment for children affected with ALL.<sup>4,5</sup> In a cytogenetic survey of childhood ALL, including 74 children with pre-B cell ALL, the distribution of patients with hypo-, pseudo-, hyper-, or normal diploid karyotypes was similar in the pre-B and "null" cell patient groups.<sup>6</sup> We have since performed chromosomal banding studies on 60 children with ALL, including "null," pre-B, B, and T cell phenotypes, and have noted the selective occurrence of a previously undescribed chromosome translocation, t(1;19), in 4 children with pre-B cell ALL. All 4 of these individuals have failed treatment, 3 within 10 mo of diagnosis. The nature of the 1;19 translocation and the demographic, clinical, and laboratory features of the children with pre-B cell ALL, with and without the t(1;19) anomaly, form the basis for this brief report.

### MATERIALS AND METHODS

#### Cell Marker Studies

After informed consent was obtained, 0.5 ml of bone marrow was aspirated, from which smears were prepared and stained with Wright-Giemsa stain for routine morphological examination to establish the diagnosis of acute leukemia and to perform FAB classification. Antiserum to common acute leukemia antigen (CALLA) was used to identify antigens common to most non-T, non-B leukemias.<sup>7</sup> Cytochemical stains, including Sudan black and periodic acid-Schiff, were performed by standard techniques.<sup>8</sup>

Immunologic classification of leukemia cells from each patient was performed as follows. Pre-B cells were identified by an immunofluorescent staining technique that permits the differential detection of surface and cytoplasmic immunoglobulin components on the same cell.<sup>1</sup> If greater than 10% of marrow blasts contained  $\mu$  heavy chains without detectable sIg, a diagnosis of pre-B cell ALL was made. Spontaneous rosette formation with neuraminidase-treated sheep erythrocytes<sup>9</sup> was used as a marker for T lymphoblasts.

#### Cytogenetic Studies

Bone marrow aspirates were cultured in RPMI 1640 supplemented with 10% fetal calf serum for 24 hr at 37°C, then exposed to colcemid (0.06  $\mu$ g/ml) for 3.5 hr at 4°C. Routine methods were employed for culture harvest, slide preparation, and GTG-banding. In addition, direct chromosome preparations were examined.

### RESULTS

Chromosomal banding studies were performed on the leukemic cells from 60 children with ALL of the following phenotypes: "null" cell, 34; pre-B, 17; B cell, 2; and T cell, 7. A unique chromosomal translocation, t(1;19)(q23;q13) was noted in leukemic cells of 4 patients with the pre-B cell ALL phenotype (Table 1) and was not seen in leukemic cells from the other 56 patients. Three distinct cytogenetic patterns were noted, each of which involved translocation of the distal one-half of the long arm (q23→qter) of chromosome 1 to the long arm of chromosome 19 in the q13 region. (This is a tentative designation because of the similar banded appearance of the short and long arms of chromosome 19.) Illustrative partial karyotypes from cases 1, 2, and 4 are shown in Fig. 1. Case 2

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**Table 1. Cytogenetic Findings for Four Patients With Pre-B Cell ALL and Chromosome 1;19 Translocation**

Patient	Clinical Status	Karyotype	No. of Cells Studied	Percent Abnormal
1	Diagnosis	46,XY,t(1;19)(q23;q13),-19, +der(19),t(1;19)(q23;q13)	22	100
	2nd Remission	46,XY	15	0
2	Diagnosis	47,XX,t(1;19)(q23;q13),+8	21	100
	1st Relapse	47,XX,t(1;19)(q23;q13),+8	18	33
3	1st Relapse	46,XX,-19,+der(19),t(1;19)(q23;q13)	30	100
	2nd Remission	46,XX	8	0
4	1st Relapse	47,XY,-19,+der(19),t(1;19)(q23;q13),+6	26	61
	2nd Remission	46,XY	15	0

displayed a form in which the translocation between chromosomes 1 and 19 appeared to be reciprocal, i.e., a normal chromosome 1 and 19 were present with a derived (der) no. 1 and a der(19). In cases 3 and 4, a normal chromosome 19 and a der(19) were present; unlike case 2, however, both no. 1 chromosomes were normal. In case 1, a normal no. 1 and a der(1) were noted along with 2 der(19) chromosomes.

Among the 13 pre-B cell patients without the t(1;19), 6 were cytogenetically normal, 5 were hyperdiploid, and 2 were pseudodiploid. Structural abnormalities of a diverse nature were identified, including t(9;22)(q34;q11), t(8;14)(q11;q32), inv(11)(p15;q23), and t(1;4)(q21;q35). No rearrangements involving chromosome 19 were noted within this group.

Clinical and immunologic features of the 4 patients with and the 13 pre-B cell leukemias without the 1;19 translocation are compared in Table 2. The patients with pre-B leukemias and a 1;19 translocation had noticeably lower white blood cell counts and, more importantly, experienced leukemic relapses much sooner than in pre-B leukemias not associated with the 1;19 translocation. The limited number of patients within each category did not permit meaningful statistical analyses of these trends.

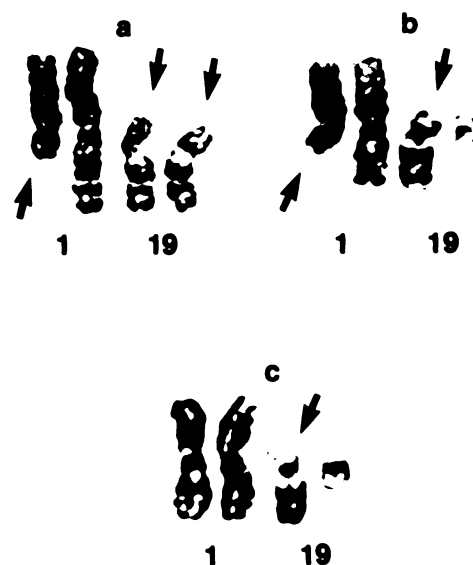
#### DISCUSSION

We have prospectively performed immunologic typing and banded chromosome analysis on the leukemic cells of 60 children with ALL and have shown that 4 of 17 children (24%) with pre-B cell ALL had a unique chromosome anomaly, t(1;19)(q23;q13). This translocation was not found in any of the 43 other cases of "null" cell, B cell, or T cell ALL, nor have we observed this translocation in any of 50 cases of chronic myelogenous leukemia or 75 cases of acute nonlymphocytic leukemia among adults or children examined during the same period of time.

Previous cytogenetic studies of patients with pre-B cell ALL have consisted largely of isolated case reports, and a number of chromosomal anomalies have been described in their leukemia cells. Two cases of

pre-B cell ALL with a 14q+ chromosome anomaly, similar to that associated with Burkitt's lymphoma, have been reported.<sup>10,11</sup> A poor outcome was noted in each of these cases. However, in a recent cytogenetic survey of 49 patients with pre-B cell ALL, none had the 14q+ anomaly, suggesting that this must be a relatively rare occurrence in patients with pre-B cell ALL;<sup>6</sup> other cytogenetic abnormalities were not detailed. Several individuals with Philadelphia chromosome (Ph<sup>1</sup>) positive chronic myelogenous leukemia have subsequently undergone a pre-B cell lymphoblastic crisis.<sup>12,13</sup>

Abnormalities of chromosome 1, particularly trisomy for all or part of the long arm, as in patients 1, 3, and 4, and trisomy for chromosome 8, as in patient 2, are relatively common in hematologic disorders. Chromosome 19 anomalies are far less common. In some patients with non-Hodgkin's lymphomas, 19p+ or 19q+ markers have been reported;<sup>14</sup> however, we are unaware of any previous report describing a t(1;19)(q23;q13) associated with chronic or acute leu-



**Fig. 1. Partial karyotypes showing chromosomes 1 and 19 from patient 1 (a), patient 2 (b), and patient 4 (c). Arrows denote the derived (der) chromosomes 1 and 19.**

**Table 2. Clinical and Laboratory Features of Patients With Pre-B Cell ALL With or Without a 1;19 Translocation**

Patient Group	Age (yr)	Sex* (M/F)	Race* (White/Black)	WBC ( $\times 10^3/\text{cu mm}$ )	Hemoglobin (g/dl)	Platelets ( $\times 10^2/\text{mm}$ )	Percent Cells Positive for			Duration† of First Remission (wk)
							slg	clg	CALLA	
4 Patients with t(1;19) (Mean $\pm$ SE)	11 $\pm$ 3	2/2	3/1	12 $\pm$ 5	10 $\pm$ 2	82 $\pm$ 29	2 $\pm$ 1	81 $\pm$ 5	74 $\pm$ 8	34
13 Patients without t(1;19) (Mean $\pm$ SE)	6 $\pm$ 1	6/7	10/3	88 $\pm$ 46	9 $\pm$ 1	115 $\pm$ 32	3 $\pm$ 1	64 $\pm$ 8	82 $\pm$ 5	66

\*Expressed as ratio.

†Projected median.

kemia. The report<sup>15</sup> of a translocation 7;19 in a child whose leukemia cells were transitional between pre-B and mature B cells is of special interest in view of the t(1;19) seen in our 4 patients. These findings may suggest a role for chromosome 19 rearrangements in some malignant disorders of B cell precursors.

Patients with Burkitt's lymphoma-leukemia, a clinically aggressive malignancy of B cell phenotype, have been shown to have a translocation involving chromosomes 8 and 14 that results in the apposition of the cellular *myc* oncogene (on chromosome 8) to that coding for  $\mu$  chain synthesis (on chromosome 14).<sup>16-18</sup> Promoter or enhancer sequences near the latter gene lead to the increased expression of the *myc* oncogene product<sup>19</sup> and possibly to the malignant cell transformation. It will be of interest to determine if cellular oncogenes are located near the chromosome breakpoints (1q23) and 19q13) noted in our patients' leu-

kemic cells. One interesting possibility is that non-munoglobulin genes integrally involved in the process of B cell differentiation may be located in one or both of these regions of the genome.

Children with pre-B cell ALL respond significantly less well to treatment than those with "null" cell ALL. They are more likely to have relapses, and the average length of their remissions is shorter.<sup>2</sup> Whereas only 7 of the 13 patients with pre-B cell ALL and no t(1;19) anomaly have relapsed over a median follow-up time of 15 mo, all 4 of our patients with the t(1;19) have failed treatment early. Two would be considered at high risk for relapse because they were over 10 yr old at diagnosis. However, none of the 4 had extreme leukocytosis or lacked CALLA expression. We suggest that this previously undescribed translocation, t(1;19)(q23;q13), marks one subgroup of pre-B cell patients who have an especially poor prognosis.

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