The t(1;14)(p34;q11) Is Nonrandom and Restricted to T-Cell Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study


We report the nonrandom occurrence, frequency, and degree of immunophenotype association of the t(1;14)(p34; q11) in children with acute lymphoblastic leukemia (ALL). This chromosomal abnormality occurred in leukemia cells from 5 of 1,630 (0.3%) consecutive children with newly diagnosed ALL who were entered on a single Pediatric Oncology Group classification study (POG 8600) between January 1986 and February 1989. The frequency of the t(1;14) was 3% (5 of 168 cases) in children with T-cell ALL. All five cases had pseudodiploid karyotypes, and in 3 cases the t(1;14) was accompanied by a deletion of the long arm of chromosome 6. This translocation is of special interest because the breakpoint on chromosome 14 in band q11 corresponds to the assigned locus of the T-cell receptor α/β chain gene. All five of our patients and three cases reported previously have had T-cell ALL. These findings, considered together, suggest that this translocation is specific for T-cell ALL and that a gene in the 1p34 region may play an important role in malignant transformation of thymocytes.

A VARIETY of cytogenetic abnormalities, particularly translocations, have been recognized as being specific for particular FAB subtypes or immunophenotypes of leukemia or lymphoma. In those conditions characterized by such translocations, it appears that expression of a proto-oncogene near one of the translocation breakpoints is altered by its reapproximation to a segment of actively transcribed DNA at the reciprocal translocation breakpoint. An example of this phenomenon is Burkitt lymphoma/B-cell acute lymphoblastic leukemia (ALL). As the result of a t(8;14)(q24; q32), the c-myc proto-oncogene on chromosome 8 is juxtaposed to the rearranged and transcriptionally active immunoglobulin (Ig) heavy-chain gene, which leads to activation and elevated expression of c-myc. The c-myc proto-oncogene has been shown to encode a nuclear protein whose function is believed to be regulation of cell growth and differentiation.

Several studies have shown that cells from patients with T-cell ALL often carry chromosomal rearrangements involving the 14q11 band, the locus of the gene encoding the T-cell antigen receptor (TCR) α/β-chain gene. At least two translocations, t(11;14)(p13;q11) and t(10;14)(q24;q11), are already known to be associated with T-cell ALL. Since TCR genes undergo rearrangement during T-cell differentiation, analogous to the rearrangement of Ig heavy-chain genes in early pre-B cells, it is reasonable to speculate that genes located at chromosome 11p13 and 10q24 may be proto-oncogenes that can be activated when altered by translocation into the region of a transcriptionally active TCR α/β-chain gene.

We report a nonrandom chromosome translocation, t(1;14)(p34;q11), which we have observed in the leukemic cells of five children with newly diagnosed T-cell ALL. Our findings suggest that this translocation is specific for T-cell ALL and that a gene on the short arm of chromosome 1 plays an important role in malignant transformation of thymocytes when altered by recombination with a TCR gene.

MATERIALS AND METHODS

Patients. Between January 1986 and February 1989, 1,630 children with newly diagnosed ALL were registered in the Pediatric Oncology Group (POG) 8600 classification study. Specimens of leukemic cells (usually bone marrow) were collected before therapy and shipped to reference laboratories for immunologic marker studies to define the major immunophenotypes of ALL (ie, early pre-B, pre-B, T-, and B-cell) and for cytogenetic characterization. Five of 168 children were identified as having both T-cell ALL and a t(1;14), and they form the focus of this study. 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. All cases were classified as to major immunophenotypes (early pre-B, pre-B, T-cell, or B-cell ALL) by using standard immunofluorescence technology with or without flow cytometry. Monoclonal reagents were uniformly used as we have previously reported. T-cell ALL was diagnosed in HLA-DR-negative cases (≥20% of blast cells positive) if more than 20% of the lymphoblasts expressed the pan-T antigen detected by CD7.

Chromosome analysis. Cell samples (usually bone marrow) were placed in sterile tubes containing RPMI 1640 supplemented with 15% fetal calf serum (FCS) and shipped overnight to the reference cytogenetics laboratory. On arrival, cells were placed in fresh medium and subjected to short-term (24-hour) culture.
Routine methods were used for culture harvest, slide preparation, and GTG-banding. Chromosomes were identified and assigned according to an International System for Human Cytogenetic Nomenclature.  

**RESULTS**

**Patients.** Table 1 presents clinical data for each of the five children with T-cell ALL and the t(1;14). All five patients were males. Complete remission was induced in all five boys after aggressive multiagent chemotherapy on a single POG protocol for children with T-cell ALL (POG 8691/8704). Four of the five have remained disease-free from 8 to 44 months.

**Immunologic markers.** Lymphoblasts from all five boys with the t(1;14) expressed CD5 and CD7 on 50% of their marrow blast cells (in one case pleural blasts were studied). All cases also expressed CD2 (E-rosette receptor), CD3 (pan-T), CD4 (T-helper), and CD8 (T-suppressor). All but one case expressed CD1 (Leu 6, thymocyte antigen) and OKT10 (antigen found on dividing cells). Four of the five cases expressed OKT9 (transferrin receptor) and CD9. Only one case expressed CD10 (CALLA antigen). Interestingly, four cases expressed one or more myeloid-associated antigens: CD15, 3; CD13 (Leu-M1), 1; CD33 (My7), 1; CD34 (My10), 2. Only one sample expressed HLA-DR antigens on a significant proportion (≥20%) of blast cells.

**Cytogenetics.** Table 2 lists the karyotypes for each of the five cases. Chromosome analyses were performed on bone marrow cells from patients 1 to 4. Cells isolated from pleural fluid were analyzed for patient 5. In each case, a pseudodip...
loid clone with a balanced 1;14 translocation was found. Three children also had deletions of the long arm of chromosome 6. In each case, the breakpoint on chromosome 1 appeared to be in the proximal portion of the p34 band and on chromosome 14 in the q11 band (Figs 1 and 2).

**DISCUSSION**

We report that 5 (0.3%) of 1,630 children with newly diagnosed ALL have an identical 1;14 translocation, t(1;14)(p34;q11). These were 5 (3%) of 168 children who had T-cell ALL, a leukemia subtype that comprises approximately 15% of newly diagnosed cases of ALL. T-cell ALL is commonly associated with a high white blood cell (WBC) count at presentation, male sex, a mediastinal mass, and an older age. Our patients are typical in this regard in that all were male, four of five had WBC counts over $60 \times 10^9/L$, four of five had a mediastinal mass, and all but one was over 7 years of age at the time of diagnosis. As expected, their disease remitted in response to aggressive multidrug induction therapy, and after follow-up times of 8 to 44 months, four of five continue in complete remission. It is too early to

![Fig 2. A complete karyotype from patient 2. The arrows indicate the approximate position of the breakpoints on the derivative chromosomes.](image-url)
1:14 TRANSLOCATION IN T-CELL ALL

accurately predict their outcome, although recent reports indicate that about 40% of such children will be cured.13,14

We are aware of several previous reports15-17 describing a total of four cases with a similar translocation, t(1;14)(p32;q11). All four were children with T-cell ALL. Despite the minor differences in interpretation of the location of breakpoints, we believe that our five patients and those from the literature have the same rearrangement. This information, considered together, suggests that the t(1;14)(p34;q11) is a relatively common nonrandom cytogenetic abnormality specific to a subgroup of children with T-cell ALL.

The 3% incidence of the t(1;14)(p34;q11) in these 168 children with T-cell ALL is comparable with the incidence of about 4% (7 of 168 cases) of the t(10;14)(q24;q11) and 6.5% (11 of 168 cases) for the t(11;14)(p13;q11), two other T-cell-associated chromosomal translocations.6,7 Leukemic cells from patients 2, 3, and 4 as well as patient KW from the literature contained an interstitial deletion of the chromosome 6 long (q) arm in addition to the t(1;14). Deletions of 6q are relatively common, occurring in approximately 5% of patients with ALL.8 Additional cases with the t(1;14) must be studied before the significance of an associated 6q deletion can be evaluated.

Several previous studies have shown that cytogenetic abnormalities involving the q11 band of chromosome 14 are nonrandom and often found in association with T-cell ALL.4-8 This association implicates these rearrangements in malignant transformation of thymocytes in all of these chromosomally defined subsets of T-cell ALL. Molecular studies of several of these translocations have shown that the break in chromosome 14 lies within the TCR b-chain gene.9,21

Kurtzberg et al17 have described a multipotential leukemic cell line (DU.528) originally derived from a pediatric case of T-cell ALL with the t(1;14)(p33;q11). It can be induced to differentiate along nonlymphoid pathways in the presence of various cytokines. This patient’s leukemic cells expressed CD7, but not CD4 or CD8. Unlike their case, all of our cases expressed both CD4 and CD8 as well as a substantial number of other T-cell associated antigens. Kurtzberg et al22 have gone on to describe eight additional cases of T-cell ALL with a similar phenotype (CD7+, CD4- , CD8+). They noted that these cases often had high WBC counts at presentation, a mediastinal mass, and skin and/or central nervous system (CNS) disease. They responded poorly to therapy, unlike our patients. The leukemic cells from seven of their eight patients could be driven to differentiate into multiple nonlymphoid lineages by hematopoietic growth factors, indicating that they appeared to be derived from multipotential hematopoietic stem cells. Cytogenetic studies demonstrated a clonal abnormality in only four of the eight cases including Kurtzberg’s previously reported case with the t(1;14). There was no common karyotype, although one additional case had an abnormality of 14q12-13. Uniform expression of CD4, CD8, and CD3 in our cases indicates a more mature thymocyte phenotype than that reported by Kurtzberg et al.17 Also, with one exception the karyotypes reported were different. Nevertheless, it is of interest that leukemic blasts from four of our five cases expressed one or more myeloid-associated antigens, suggesting a mixed lineage.

Information regarding the molecular pathogenesis of T-cell ALL with t(1;14) has recently been reported. Begley et al23 reported that a fusion transcript resulted from the t(1;14) with segments derived from each chromosome in the cell line reported by Kurtzberg et al,17 and suggested the name, SCL (stem-cell leukemia), for a putative gene identified by this translocation. They further commented that the predicted SCL protein product had primary amino acid sequence homology to the previously described amphipathic helix-loop-helix DNA binding and dimerization motif for enhancer binding proteins.24 Similar conclusions were reached by Finger et al25 who studied the same cell line and named the putative gene, TCL5. More recently Chen et al26 have isolated the breakpoint junctions of the 1;14 translocation from two of our patients (patients 4 and 5) and defined the breakpoints in both. On chromosome 14, the breakpoints occurred within the TCR b-chain gene. The breakpoints on chromosome 1 occurred within a kilobase of each other, suggesting that they represent a genetic locus (tal) involved in leukemogenesis. Further, they defined an exon within tal (SCL, TCL5) that potentially encodes a protein similar to that described above (ie, a helix-loop-helix motif similar to that found in a variety of DNA binding proteins including the products of the MyoD1 gene, the myogenin gene, the E12/E47 enhancer binding proteins, and the products of the myc and hlx-1 oncogenes). These investigators concluded that, since this motif plays a demonstrated role in DNA binding, the tal gene product may influence leukemic development by direct interaction with DNA.

Our study suggests that the t(1;14)(p34;q11) is specific for T-cell ALL with a frequency of approximately 3% among children with this malignancy. Consistent with what is known about other nonrandom translocations, the repeated observation of specific breakpoints on chromosomes 1 and 14 suggests that genes at or near these sites play an important role in malignant transformation/proliferation of thymocytes.

REFERENCES

8. Croce CM, Isobe M, Palumbo A, Puck J, Ming J, Tewary D,


19. McKeithan TW, Shima EA, Le Beau MM, Minowada J, Rowley JD, Diaz MO: Molecular cloning of the breakpoint junction of a human chromosomal 8;14 translocation involving the T-cell receptor α-chain gene and sequences on the 3′ side of MYC. Proc Natl Acad Sci USA 83:6636, 1986


The t(1;14)(p34;q11) is nonrandom and restricted to T-cell acute lymphoblastic leukemia: a Pediatric Oncology Group study

AJ Carroll, WM Crist, MP Link, MD Amylon, DJ Pullen, AH Ragab, GR Buchanan, RS Wimmer and TJ Vietti

Updated information and services can be found at:
http://www.bloodjournal.org/content/76/6/1220.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml