CONCISE REPORT

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

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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 t dic(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 t dic(9;12) but was absent in the other seven. Our results suggest that the t dic(9;12)(p11?p12) rearrangement is specifically associated with leukemic B cell precursors.

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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 t dic(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
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 x 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.6,9

We are aware of only two other reports of a similar 9:12 translocation. The LAZ221 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,
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 oncogene has been mapped to 12p11.1-12.1, molecular studies of cases with the tdic(9;12) appear warranted.

The clinical significance of the tdic(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 translocation1 or hypodiploidy30 confers a poor prognosis suggest that patients with the tdic(9;12) are at increased risk for treatment failure; however, longer follow-up is required to substantiate this impression.

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