An Analysis of Leukemic Cell Chromosomal Features in Infants

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Leukemic cell chromosomal findings in 27 infants were analyzed. Among the 18 cases of acute nonlymphoblastic leukemia (ANLL), all but two were classified as monocytic or myelomonocytic. The remaining nine cases were acute lymphoblastic leukemia (ALL), seven lacking the common ALL antigen and two having cytoplasmic immunoglobulin (pre-B phenotype). Twenty-five cases (93%) had an abnormal karyotype, 21 (84%) being pseudodiploid. Chromosomal translocations were detected in 67% of the ANLL cases and in 78% of the ALL cases. Nonrandom chromosomal abnormalities included the t(9;11) in 78% of the ALL cases. Nonrandom chromosomal translocations were detected in 67% of the ANLL cases and in 78% of the ALL cases. Nonrandom chromosomal abnormalities included the t(9;11)(p21-22;q23) in three cases of monocytic leukemia, inversion of chromosome 16 in three cases of myelomonocytic leukemia with bone marrow eosinophilia, and t(4;11)(q21;q23) in one case of ALL. Chromosomal regions preferentially involved in infant leukemia included 11q23-25 (13 cases), 9p21-22 (6) and 10p11-13 (3). All but one of the 24 cases with chromosomal breakage or rearrangement had breakpoints that corresponded to known fragile sites, half of which were at 11q23-25, a finding that may have pathogenetic importance. The CALLA or pre-B phenotype and the presence of chromosomal translocations in most infants with ALL provide a biological explanation for their poor prognosis.

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CNS leukemia at diagnosis and at relapse. Only six of these patients remain in remission, for 6+ to 47+ months.

CALLA+, so-called undifferentiated (HLA-DR* only), ALL was diagnosed in seven infants and pre-B ALL (positive cytoplasmic immunoglobulin) in two, one of whom was CALLA+. In case 20, two thirds of the blasts had LI morphology, and the remainder resembled monoblasts, although the α-naphthyl butyrate esterase stain was negative. A lymphoid-associated antigen, B4, was present on 65% of blast cells and the myeloid-associated antigen My-9 on 39% of blasts. Leukocyte counts in cases of ALL ranged from 8.5 to 201 x 10⁹/L (median, 90 x 10⁹/L), platelet counts from 7 to 354 x 10⁹/L (median, 42 x 10⁹/L), and hemoglobin levels from 4.9 to 11.2 g/dL (median, 8.7 g/dL). Four infants had CNS leukemia at diagnosis; none had a mediastinal mass. Two of the nine patients remain in remission for 14+ and 26+ months.

Of the 18 cases of ANLL, 16 (89%) had leukemic cell chromosomal abnormalities (Fig 1). The most frequent structural abnormalities were translocations (12 cases, 67%), inversions (three cases), and deletions (two cases). Whole chromosome additions were noted in two cases, including patient 6 (a child with Down’s syndrome); none of the cases showed a loss of whole chromosomes. The structural abnormalities most frequently involved chromosomes 11 (ten cases), 9 (five cases), 16 (four cases), and 10 (four cases).

The chromosomal regions most commonly affected were 11q23-25 (seven cases), 9p21-22 (four cases), 11q12-13 (three cases), 16p13 (three cases), 16q22 (three cases), and 10p11-13 (two cases). Nonrandom chromosomal abnormalities included t(9;11)(p21-22;q23) in three cases of monocytic leukemia and inversion at bands p13 and q22 of chromosome 16 in three cases of myelomonocytic leukemia with bone marrow eosinophilia.

All nine infants with ALL had blast cell chromosomal abnormalities (Fig 2): pseudodiploidy in seven cases, hypodiploidy with 45 chromosomes in one, and hyperdiploidy with 47 chromosomes in one. Translocations were observed in seven cases (78%), of which six involved 11q23-25 and two involved 9p21.

In both ANLL and ALL, chromosomes 11, 9, and 10 were frequently involved in structural rearrangements, mainly translocations. The common breakpoints were 11q23-25 (13 of 27 cases, 48%), 9p21-22 (six cases, 22%), and 10p11-13 (three cases, 11%).

**DISCUSSION**

Chromosomal rearrangements involving 11q23-25 were the most frequent finding in this study of infant leukemia, affecting half of our patients. This contrasts with the much lower frequency of 11q23-25 rearrangements in consecutive cases of childhood ALL (4% of 230 cases) or ANLL (13% of...
The other frequent abnormality involving 11q23 was t(9;11)(p21;q23), a nonrandom abnormality that is known to be associated with monocytic or myelomonocytic leukemia,\(^15\) the two commonest ANLL subtypes in infants.\(^2,\) Case 21 [ALL with the t(9;11)(p21;q23)] is interesting in that most of the blasts appeared to be lymphoid, with a small proportion resembling monoblasts. The findings of both B4 and My-9 positivity in blast cells support the mixed-lineage antigen expression of her leukemia. Kaneko et al\(^12\) also reported this chromosomal abnormality in two cases of CALLA ALL, one of which occurred in an infant. Thus t(9;11)(p21;q23) is not only found in monocytic or myelomonocytic leukemia but also in CALLA ALL, including some cases with mixed-lineage antigen expression. Rearrangements involving 11q23-25 are in general common findings in CALLA- ALL.\(^21\) Some cases of CALLA- ALL are characterized by myeloid-associated antigens;\(^22\) in others the blast cells have been induced to differentiate in the myeloid pathway.\(^23\) Taken together, these findings support the idea of preferential transformation of pluripotent stem cells with 11q23 involvement in infants and suggest that genes from the reciprocally translocated chromosome influence subsequent phenotypic expression.\(^1,2,21\) Recently we found an 11q23 translocation at relapse in each of several cases that had converted from common or pre-B ALL at diagnosis to CALLA ALL (three cases) or ANLL (three cases) at relapse.\(^24\) We have suggested that these cases represent emergence of a malignant pluripotent stem cell after eradication of the original B-cell precursor or pre-B leukemic stem line by chemotherapy.

Four of 29 cases of infant leukemia reviewed by Abe et al\(^7\) had abnormalities involving chromosome 10, including three cases with a breakpoint at 10p11-13. Recently, another case of congenital monoblastic leukemia with del(10) (p12) was reported.\(^25\) In this study four of 27 cases were found to have chromosomal abnormalities involving chromosome 10; in three cases the breakpoints were in the 10p11-13 region. By contrast, of 380 children with acute leukemia studied at this center, only five over a year of age had blast cell chromosomal rearrangement affecting this region \((P = 0.01\) by two-tailed Fisher exact test) (SC Raimondi and DL Williams, unpublished observation). Thus, the 10p11-13 region can be added to those known to be preferentially involved in infant leukemia.

The breakpoints in all but one of the 24 cases with chromosomal rearrangements (case 17) corresponded to known heritable or common fragile sites or both.\(^26-28\) In 18 cases the breaks occurred at one or two heritable fragile sites, 13 being at 11q23 (FRA11B), five at 9p21 (FRA9A), three at 16q22 (FRA16B), and one each at 11q13 (FRA11A) and 12q13 (FRA12A). Confirmation of the putative association between heritable fragile sites and chromosomal breakpoints in infant leukemia will require further study of normal cells from the patients and their family members. Recently several studies have shown a concordance between heritable fragile sites and the breakpoints involved in chromosomal rearrangements in leukemia and lymphoma.\(^29-32\) Hecht and Sutherland\(^33\) found a statistically significant association between 21 fragile sites and 50 cancer breakpoints. It has been suggested that oncogenes or other very active genes may be located at or near hypersensitive or fragile sites where carcinogens can act, resulting in chromosomal breakage and rearrangement leading to malignant transformation.\(^23\) Since infants are less likely than older patients to have experienced a carcinogenic event followed by a latency period adequate for the development of cancer, we speculate that acute leukemia in infants arises from constitutional or developmental genetic errors occurring at critical points in hematopoietic cellular ontogeny and differentiation.

Most of our cases had chromosomal breakpoint(s) where oncogene(s) have been mapped.\(^34\) Since the c-ets-1 protooncogene has been traced to 11q23\(^35\) and half of our cases have breakpoints in this region, it is possible that c-ets-1 is frequently involved in the pathogenesis of infant leukemia.
Rovigatti et al have recently demonstrated amplification and rearrangement of this oncogene in a case of acute myelomonocytic leukemia and in a case of small lymphocytic-cell lymphoma with 11q23 involvement. It is also intriguing to note that α- and β-interferon genes have been localized to 9(p21 → pter), a region commonly involved in infants with leukemia.

One of the most important prognostic factors in childhood ALL is age at diagnosis. Even after adjustment for other presenting features, a very young age remains an independent predictor of poor outcome. However, in most studies leukemic cell chromosomal analyses have generally not been included, and their independent contribution to prognosis has not been assessed. In our most recent study, the frequency of translocation was 40% among 116 consecutive children with newly diagnosed ALL. The high frequency (78%) of leukemic cell chromosomal translocations found in this study provides a biological explanation for the poor outcome of infants with ALL. Translocations in general appear to confer a poor prognosis in ALL. The risk of early relapse was six times greater when a translocation was present, making this feature the strongest single predictor of outcome. Notably, hyperdiploidy with >50 chromosomes, a favorable feature found in approximately 30% of childhood ALL cases, was not found in any infant in this series or in the review by Abe et al.

We conclude that most cases of infant leukemia are characterized by leukemic cell chromosomal abnormalities involving 11q23. The preferential involvement of 11q23 chromosomal region, the relationship between the breakpoints of reported fragile sites, and the likely minimal exposure of infants to environmental mutagens and carcinogens suggest a different mode of leukemogenesis in this young age group compared with older patients. Moreover, the poor outcome of infant ALL can be explained not only by their large leukemia cell burden and unfavorable immunophenotype but by the lack of leukemic cell hyperdiploidy and the frequent presence of chromosomal translocations. Finally, the definition of specific chromosomal anomalies in the blasts from infants with acute leukemia should provide direction for molecular studies that hold the exciting promise of unravelling the pathogenesis of these disorders.

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