CONCISE REPORT

Leukemia with Down's Syndrome: Translocation Between Chromosomes 1 and 19
In Acute Myelomonocytic Leukemia Following Transient Congenital Myeloproliferative Syndrome

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A girl with Down's syndrome was born with a myeloproliferative disorder. The child had spontaneous regression of the myeloproliferation, with acute leukemia developing at a later date. Morphologic, cytochemical, immunologic, and immunoglobulin gene configuration studies all supported the diagnosis of acute nonlymphocytic leukemia. High-resolution chromosome studies revealed that the leukemic cells consistently contained a translocation between chromosomes 1 and 19: der(19)(t(1;19)(q25;p13). Spontaneous regression of the transient myeloproliferative syndrome of the newborn with Down's syndrome may not always be permanent, and the transient myeloproliferative syndrome may sometimes represent an early sign of acute nonlymphocytic leukemia.

CASE REPORT

A newborn girl had typical clinical findings of Down's syndrome with marked hepatosplenomegaly. A complete blood count at 20 hours of age revealed a white blood cell count of 55,000/μL with 6% lymphocytes, 12% polys, 15% bands, 2% monocytes, and 65% blast forms. The blast forms included myeloblasts, erythroblasts, and megakaryoblasts. Megakaryocyte fragments were noted in the peripheral blood. The hemoglobin level was 13.9 gm/dL, the hematocrit value was 39%, and the platelet count was 208,000/μL. A bone marrow aspirate revealed normal maturation of all cell lines without petechiae developed. A peripheral blood count revealed thrombocytopenia, and a bone marrow aspirate showed normal maturation of all cell lines. Over the ensuing 6 months, thrombocytopenia persisted, and leukopenia and a macrocytic anemia were noted. A bone marrow aspirate at 25 months of age revealed 25% blast forms and some dyserythropoietic changes. A repeat bone marrow aspirate at 28 months of age disclosed total effacement of the bone marrow by a population of blast cells with the features of myelomonocytic leukemia. The patient received no specific antileukemic therapy, and she died at 31 months of age.

RESULTS

Cytogenetic studies were performed several times during the course of this patient's illness. All other studies to be described were performed on cells obtained from a bone marrow aspirate obtained at 28 months of age in which more than 85% of nucleated cells in the marrow were leukemic blasts.

Cytochemical Studies

The blast cells were strongly positive with histochemical stains for nonspecific esterase, Sudan black, and peroxidase.

Immunologic Studies

Reactivity of the bone marrow blast cells with panel murine antileukocyte monoclonal antibodies was assayed by an indirect immunofluorescence technique using a fluorescence-activated cell sorter for analysis. The bone marrow aspirate revealed normal maturation of all cell lines without evidence for replacement by leukemia. A diagnosis of myeloproliferative syndrome was made, and no specific therapy was given. The baby appeared well and thrived, and, by the age of 9 months, the peripheral blood picture was entirely normal.

Immunoglobulin Gene Rearrangement Studies

The status of the immunoglobulin heavy-chain genes was assessed by previously described methods. Briefly, DNA from blast cells was extracted, digested with restriction enzymes, size fractionated on agarose gels, Southern blotted, and hybridized with the human J_H immunoglobulin gene probe. The immunoglobulin heavy-chain genes were found to be in germ line configuration.
Cytogenetic Studies

Peripheral blood lymphocytes obtained after birth were stimulated with phytohemagglutinin for three days. The cells demonstrated 47,XX,+21 (trisomy 21), with no other cytogenetic abnormalities. However, banding studies were not performed.

Cytogenetic studies of bone marrow aspirates obtained when the patient was 22, 25, and 28 months of age were studied by high resolution G-banding following methotrexate synchronization and thymidine release. In these studies, a minimum of 15 cells was analyzed from each sample. At 22 months of age, two cell lines were noted: (1) a cell line with 47,XX+21 and (2) another line with translocation between chromosomes 1 and 19 in the place of a normal chromosome 19: 47,XX+21, −19+der(19)t(1;19)(q25;p13) (Fig 1). At 25 months of age, a third cell line in addition to these two was observed together with an extra X and an extra chromosome 8: 49,XXX,+8,+21, −19,+der(19)t(1;19)(q25;p13). At 28 months of age, when the marrow was completely effaced, all cells demonstrated the 1;19 translocation. Clones containing the extra X and extra chromosome 8 were no longer evident.

DISCUSSION

The nature of the transient myeloproliferative syndrome associated with Down's syndrome has been the subject of continued controversy. Whether this syndrome results from the ineffective regulation of myelopoiesis or spontaneous, prolonged remission of true congenital leukemia is uncertain.1-4 Although the majority of affected children apparently recover completely, several reports of the development of true acute leukemia in children who had prior resolution of the transient myeloproliferative syndrome5 (as in the patient reported here) suggest that the transient myeloproliferative syndrome may represent true, spontaneously remitting acute leukemia. Careful cytogenetic studies with banding in cases of transient myeloproliferative syndrome may help elucidate this controversy since clonal karyotypic abnormalities detected in the presence of the myeloproliferative syndrome in the newborn period might be seen to disappear with spontaneous remission and recur with the development of full-blown acute leukemia. Unfortunately, banding studies were not performed in this patient on bone marrow cells obtained in the newborn period.

The chromosomal abnormality observed in the leukemic cells of this patient was a translocation between chromosomes 1 and 19. This translocation has not been previously reported, to our knowledge, in acute nonlymphocytic leukemia, although a translocation between chromosomes 1 and 19 has been reported in cases of pre-B cell acute lymphoblastic leukemia.10-13 There is little doubt that the leukemia seen in this patient derived from cells of myeloid lineage based upon the results of morphologic, cytochemical, immunologic, and gene rearrangement studies. Furthermore, it is unlikely that this patient had biphenotypic leukemia with a small population of cells of lymphoid lineage (pre-B cells) accounting for the translocation since a clonal population of cells of B lineage accounting for as few as 1% of the total cells can be detected by gene rearrangement studies.14 Moreover, the break points in chromosome 1 in cases of pre-B acute lymphocytic leukemia were in bands q21 or q23 (proximal to the break point in our case) and in chromosome 19 in bands p13 or q13. A single case of acute undifferentiated leukemia has been reported with a t(1:19) translocation,15 with the break point in chromosome 1 being in the region of bands q23 to q25.

One cell line from our patient exhibited 49 chromosomes
including trisomy 8, a cytogenetic abnormality often associated with acute nonlymphocytic leukemia\textsuperscript{16} as well as trisomy X. Karyotype abnormalities in other cases of acute leukemia in Down’s syndrome are reviewed critically elsewhere.\textsuperscript{3,4}

We would propose that this child with Down’s syndrome and transient congenital myeloproliferative syndrome may have had a true congenital acute myelomonocytic leukemia. A spontaneous remission of almost 2 years duration was interrupted by manifestations of preleukemia and subsequently frank leukemic relapse at 28 months of age. Had appropriate chromosome studies been done on the blast cells during the neonatal period, we expect that the marker t(1;19) translocation would have been observed at that time. Certainly, prospective longitudinal cytogenetic studies of children with the transient myeloproliferative syndrome are likely to be very informative.

The constitutional trisomy 21 in this case might be considered as a chromosome abnormality predisposing to leukemia,\textsuperscript{17} the acquisition of the translocation between chromosomes 1 and 19 might be viewed as a key leukemogenic event on a chromosomal level, and the addition of chromosome 8 and the X might be seen as part of the biologic evolution of this leukemia.

REFERENCES

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