Acute Leukemia With C-G Chromosome Translocation

By Elliott Hinkes, Barbara F. Crandall, Felice Weber, and Charles G. Craddock

The occurrence of acute lymphocytic leukemia in a young man with a C-G translocation is described. Two members of his family also show C-G translocations but have not as yet developed leukemia. A third member of the family, on whom no chromosomal information was available, died of acute lymphocytic leukemia.

Cytogenetic abnormalities in patients with leukemia have been reported with increasing frequency as more careful chromosomal studies have been performed. While only chronic myelogenous leukemia (CML) is characterized by a specific chromosomal marker (the Philadelphia chromosome, Ph1), a significant percentage of all morphologic types of leukemia, except possibly chronic lymphocytic leukemia, will demonstrate aneuploidy.

This report describes the occurrence of acute lymphocytic leukemia (ALL) in a young man with a balanced C-G translocation, t(Cp-; Gp+), a rare chromosomal abnormality not previously described in patients with leukemia. The study includes data on the hematologic and cytogenetic status of the patient’s family, one member of which also died of ALL and two members of which demonstrated C-G translocations without leukemia.

CASE REPORT

DB, a 27-yr-old white male, was referred to UCLA in September 1970 for chromosomal analysis, following discovery of an abnormal karyotype in his daughter. The daughter (TB), born in November 1968, was evaluated at UCLA for mental retardation and a peculiar physical appearance characterized by small size and weight (less than third percentile), low set ears and a high vaulted head, broad hands with simian lines and short broad thumbs, and shortened in-curved fifth fingers. Clinical impression was Rubenstein-Taybi syndrome, but subsequent chromosomal analysis revealed an abnormality of one chromosome of the G group. Chromosomal analysis of the phenotypically normal father (DB) revealed a balanced C-G translocation.

In October 1970, DB was referred to one of us (CC) for evaluation of weakness, easy bruisability, and nasal bleeding. Physical examination revealed a febrile young man with petechiae, epistaxis, generalized lymphadenopathy, and striking hepatosplenomegaly. Hematocrit was 44% with platelets 3000/cu mm and white count 83,000/cu mm, including...
51% lymphocytes and 40% blast cells. Admission creatinine was 7 mg/100 ml. Shortly after admission the patient became anuric, necessitating hemodialysis on two occasions. After confirmation of the diagnosis of ALL with a bone marrow examination that revealed sheets of lymphoblasts, the patient was treated with prednisone, 6-mercaptopurine, and vincristine. Chromosomal studies were repeated. By late October 1970, the patient was felt to be in complete symptomatic and hematologic remission and so was discharged from the hospital on 6-mercaptopurine and prednisone maintenance therapy.

In early December 1970, DB was readmitted to UCLA complaining of facial weakness. Physical exam revealed recurrence of lymphadenopathy and splenomegaly and the appearance of papilledema and multiple cranial nerve palsies. Hematocrit was 32%, while count was 3900/cu mm with a normal differential, and platelets were 330,000/cu mm. Spinal fluid revealed 1800 white cells/cu mm, the great majority of which appeared to be blast cells. The patient was treated with high-dose steroids and intrathecal methotrexate, the latter given as five intrathecal injections totaling 80 mg. By early January 1971, the patient was again felt to be in remission and was placed on maintenance intramuscular methotrexate. By late January 1971, adenopathy recurred, and the patient was treated with prednisone, vincristine, and finally Cytoxan. Despite this, the patient’s condition deteri-
Chromosome loss appeared to be random.

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Fig. 3. Full karyotype of TB (III-1). Arrow shows the G group chromosome carrying extra material on short arm. C group appears to be normal.

orated, as terminally he developed severe hepatitis. In mid-March 1971, approximately 5 mo after diagnosis, he died.

Family Studies

The family pedigree is outlined in Fig. 1. DB's mother (I-2) died elsewhere at age 47 of acute leukemia, several years before the death of DB (II-4). No chromosomal data are available, but review of blood smears and bone marrow preparations by the authors revealed changes compatible with ALL.

Chromosomal analysis of DB (II-4) (Fig. 2) was performed on peripheral blood lymphocytes (with phytohemagglutinin) 1 mo prior to the diagnosis of ALL and revealed the abnormal karyotype 46,XY,t(Cp-;Gp+). Repeat studies, performed in early and late October, of bone marrow during the blastic phase and of skin during remission both revealed 46,XY,t(Cp-;Gp+) (Table 1).

Chromosomal analysis of the peripheral blood of daughter TB (III-1) on three occasions revealed additional material on the short arms of a G group chromosome, 46,XX,Gp+ pat (Fig. 3). Fluorescent microscopy with quinacrine mustard identified the affected G chromosome as a No. 22. The fact that TB is partially trisomic for the short arms of a No. 12 chromosome was deduced from the studies on RB.

Chromosomal studies on peripheral blood lymphocytes of RB (III-2), the sister of TB (III-1), showed the same chromosomal rearrangement as her father, DB (II-4). Since she is phenotypically normal, she appears to have a balanced translocation. Fluorescent microscopy identified the affected G group chromosome as No. 22 and the affected C group chromosomes as No. 12 (Fig. 4). Material has been translocated from the short arms of No. 12 to the short arms of No. 22.

Chromosome analyses of DB's brother (II-1), his wife (II-5), and his father (I-1) were all normal.

RESULTS AND DISCUSSION

Chromosome abnormalities, most in the form of acquired abnormalities, have been described in about 50% of cases with acute leukemia, although the incidence in individual studies varies greatly. Aneuploidy and pseudo-

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<td>Bone marrow 2</td>
<td>Oct. 16, 1970</td>
<td>34 1</td>
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*Chromosome loss appeared to be random.
diploidy are found most frequently, with the modal chromosome number ranging in one study\textsuperscript{1} from 41 to 53 in acute myelogenous leukemia (AML) and from 46 to over 90 in ALL. Hypodiploidy is said to be uncommon in ALL as compared with AML, while "fuzzy" chromosomes with poorly defined morphology are said to be more characteristic of ALL. Hypodiploidy in acute leukemia may be associated with a poorer prognosis, whereas extra D or E chromosomes may be associated with a better prognosis.\textsuperscript{5} There may be an increased incidence of C and G group abnormalities,\textsuperscript{1,4,6,7} especially C trisomy, but since the C group is the largest, this might be expected. The possibly increased incidence of abnormal G group chromosomes in leukemia patients is of interest, however, as both the Ph\textsuperscript{1} chromosome (a deletion of No. 22) in CML and the supernumary chromosome (No. 21) in Down's syndrome affect this relatively small chromosomal group. Unlike cases of CML, the karyotypic abnormalities in the acute leukemias tend to disappear in remission, usually to reappear in relapse.\textsuperscript{1,8}

The case reported here is unique in that this relatively rare karyotypic abnormality—balanced C-G translocation—has not been previously noted in association with leukemia. In fact, the balanced translocation is apparently not associated with any phenotypic abnormalities, while the unbalanced translocation (as seen in TB), has, in the ten cases reported so far, been associated with mental retardation, a variety of congenital abnormalities, or occasionally Down's syndrome,\textsuperscript{9-11} but not leukemia. The mental retardation and physical abnormalities seen in TB are probably due to the unbalanced C-G translocation, rather than Rubenstein-Taybi syndrome as first thought, since chromosomal abnormalities in the latter syndrome are rarely noted.\textsuperscript{12-14} The other daughter, R.B., shows, as expected, no phenotypic abnormalities associated with her balanced C-G translocation.

The relationship between DB's chromosomal aberration and his subsequent development of ALL can only be speculated on. The death, also from ALL, of DB's mother on whom no chromosomal information was available is interesting, since the translocation was either transmitted through her (in view of the normal karyotype of I-1) or arose de novo in DB. This coincidence of C-G translocation and leukemia suggests that other patients with C-G translocation be followed closely from a hematologic standpoint. To
date, there is no evidence of leukemia in other members of this family, although long-term follow-up is anticipated.

ACKNOWLEDGMENT

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REFERENCES

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