Transformation of Fanconi’s Anemia to Acute Nonlymphocytic Leukemia Associated With Emergence of Monosomy 7

By Timothy J. Stivrins, Richard B. Davis, Warren Sanger, Jene Fritz, and David T. Purtilo

Two sisters in whom a diagnosis of Fanconi’s anemia was made at ages 12 and 18 subsequently developed acute nonlymphocytic leukemia (ANLL). A third sibling had previously died at age 11 of apparent sepsis. Both sisters had cytogenetic studies that showed increased chromosomal breakage and a 46,XX karyotype, but subsequently developed ANLL after, or coincident with, the emergence of monosomy 7. These observations suggest that, in addition to myelodysplastic syndromes and defective neutrophil chemotaxis, monosomy 7 may be associated with the emergence of leukemia in this disorder.

FANCONI’S ANEMIA is an autosomal recessive disorder characterized by pancytopenia, hyperpigmentation, frequent malformations of skeletal structure, small stature from birth, and hypogonadism. In addition, at least 17 patients, including the cases reported here, have developed acute leukemia. Cytogenetic changes occur in the majority of patients with acute nonlymphoblastic leukemia. Cytogenetic alterations in Fanconi’s anemia with acute leukemia have been incompletely documented, however. We report two sisters with classic manifestations of Fanconi’s anemia who developed monosomy 7, coincident with the development of acute nonlymphocytic leukemia (ANLL). The possible role of monosomy 7 and chromosomal breakage in the development of ANLL is discussed.

CASE REPORTS

Case 1

A diagnosis of Fanconi’s anemia in a 12-year-old girl was made in 1967, based on progressive anemia and thrombocytopenia (erythrocyte count 3.5 x 10^6/μL, platelets 43,000/μL), cutaneous hyperpigmentation, mild bilateral lenticular hypoplasia, syndactylism of the second and third toes bilaterally, retarded growth rate, and short stature (150 cm). One sister died in 1969 at age 11, apparently of sepsis.

In May 1979, the patient experienced acute gastrointestinal and mild central nervous system hemorrhage. Blood platelets and packed red cell transfusions, oxymethalone (50 mg 3 times a day), and prednisone (50 mg daily) were given. She was discharged on the 27th hospital day with a hemoglobin of 14.6 g/dL, platelets 12,000/μL, leukocyte count 4,800/μL, with 10% neutrophils, 15% bands, 61% lymphocytes, and 14% monocytes. Three weeks later she became jaundiced. Androgenic steroids were withdrawn and liver function improved. She was monitored as an outpatient with treated red cell and platelet transfusions, and prednisone. In February 1980, her hemoglobin was 11.7 g/dL and platelets 177,000/μL. She was maintained on prednisone, 60 mg daily.

In July 1980, her leukocyte count was 5,700/μL (with 10% segmented neutrophils, 6% bands, 66% lymphocytes, 5% monocytes, and 13% blast cells), hemoglobin was 11.6 g/dL, and platelets were 593,000/μL.

A bone marrow aspirate in August 1980 showed 80% cellularity with 12% blast forms. Sudan black B and peroxidase reactions of the blast cells were unreactive. A periodic acid-Schiff stain showed a finely speckled positivity about the nuclei, but not a coarse clumped staining pattern. In October 1980, the leukocyte count was 23,300/μL, with 15% neutrophils, 4% bands, 17% lymphocytes, 3% monocytes, 1% eosinophils, 1% metamyelocytes, and 59% blast forms. Hemoglobin was 13.4 g/dL and platelets were 450,000/μL. Karyotypes of bone marrow and peripheral blood on Oct 14, 1980 revealed a 45,XX,−7/46,XX female chromosomal complement, with 20% (8/40) of the metaphase plates showing random chromosome breakage. Her karyotype in 1979 had shown a 46,XX complement with 14% (3/21) of the metaphase plates having random chromosomal breakage.

Chemotherapy with 6-thioguanine, daunorubicin, cytarabine, and prednisone was given for six cycles. The total dose of 6-thioguanine was 1.6 g, of daunorubicin 200 mg, of cytarabine 2.1 g, and of prednisone 900 mg. Her course was complicated by intermittent bacterial and fungal infections. Remission was not obtained, and in April 1981, her leukocyte count was 55,000/μL with 87% blast cells. In May 1981, she died in her home community of an intracerebral hemorrhage.

Case 2

The younger sister of the proband was pancytopenic (leukocyte count of 3,000/μL, with 7% neutrophils, 3% bands, 86% lymphocytes, and 4% monocytes; hemoglobin 8.5 g/dL, and platelets of 108,000/μL) in December 1979, at age 18.

In November 1980, chromosomal analysis of peripheral blood lymphocytes showed a 46,XX female chromosome complement with 20% (4/20) of the metaphase plates showing random chromosomal breakage. She was treated with fluoxymesterone and prednisone, and was returned to the care of her home physician. Eleven months later, she developed malaise, and drug abuse was reported. Leukocytes numbered 2,100/μL, with 2% neutrophils, 1% bands, 86% lymphocytes, and 10% monocytes. Her hemoglobin was 5.7 g/dL, reticulocytes were less than 2,000/μL, and platelets were 38,000/μL. She was given red cell and platelet transfusions and was hospitalized with abdominal pain. A ruptured ovarian cyst was resected. The ovaries were diminutive (2 x 1 x 1 cm) and the uterus was 3 cm in length. A second chromosome analysis in November 1981, on bone marrow, revealed a 45,XX,−C/46,XX chromosome complement.

From the Departments of Internal Medicine, Human Genetics, and Pathology and Laboratory Medicine, University of Nebraska Medical Center, Omaha.

Supported in part by National Institute of Health grant CA 30196 (to D.T.P.), American Cancer Society grant RD-161, and Nebraska Cigarette Tax grant LB506 (to D.T.P. and W.S.).

Address reprint requests to Dr Timothy J. Stivrins, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68105.

© 1984 by Grune & Stratton, Inc.

In April 1982, her leukocyte count was 1,900/μL, with 2% neutrophils, 2% bands, 85% lymphocytes, 5% monocytes, and 16% blast cells. Hemoglobin was 10.7 g/dL, and the platelets were 5,700/μL, less than 8,000/μL. Bone marrow biopsy revealed an hypoplastic marrow with less than 5% cellularity.

The patient’s final admission occurred in May 1982 for fever. During this admission, a karyotype from unstimulated peripheral blood cultures revealed a 45,XX,-7/46,XX chromosome complement, with 22% (5/23) of metaphase plates showing increased chromosomal breakage. After resolution of the fever, the patient elected to return home; she died in June 1982.

**DISCUSSION**

Miller has noted two major pathogenetic mechanisms that predispose to malignant lymphoma or to ANLL. Patients with cellular immune defects can develop Epstein-Barr virus-induced lymphomas. In contrast, patients with chromosomal breakage syndromes, including Fanconi’s anemia, tend to develop ANLL. Ultimately, a cytogenetic alteration may provide a final common pathway to all hematologic malignancies.

The following sequence of events had occurred in the sisters reported here: an inherited pleiotropic autosomal recessive trait was manifested as syndactyly at birth. Later, growth retardation, short stature, hyperpigmentation, ovarian hypoplasia, and ANLL evolved (Table 1).

At least 15 patients with Fanconi’s anemia have previously been reported to have developed ANLL (Table 2). All patients evaluated had prior chromosomal breakage. Impaired ability to repair DNA cross-links after exposure to mitomycin C in cultured fibroblasts, including Fanconi’s anemia, tend to develop ANLL. Ultimately, a cytogenetic alteration may provide a final common pathway to all hematologic malignancies.

**Table 1. Serial Cytogenetic Studies**

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Date</th>
<th>Tissue*</th>
<th>Metaphase Plates With Random Breaks</th>
<th>Number of Cells</th>
<th>Chromosome Complement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>May 1979</td>
<td>BL-S(72)</td>
<td>3 of 21</td>
<td>0</td>
<td>46, XX</td>
</tr>
<tr>
<td></td>
<td>July 1980</td>
<td></td>
<td>Blasts appear on peripheral smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>October 1980</td>
<td>BL-U(24)</td>
<td>1 of 2</td>
<td>2</td>
<td>45,XX, -C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BL-S(72)</td>
<td>3 of 18</td>
<td>8</td>
<td>45,XX, -7/46, XX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM(24)</td>
<td>4 of 20</td>
<td>7</td>
<td>45,XX, -7/46, XX</td>
</tr>
<tr>
<td>2</td>
<td>November 1980</td>
<td>BL-S(72)</td>
<td>4 of 20</td>
<td>0</td>
<td>46,XX</td>
</tr>
<tr>
<td></td>
<td>November 1981</td>
<td>BM(D)</td>
<td>0 of 5</td>
<td>3</td>
<td>45,XX, -C/46, XX</td>
</tr>
<tr>
<td></td>
<td>April 1982</td>
<td>BM(24)</td>
<td>No mitotic cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May 1982</td>
<td>BL-U(24)</td>
<td>5 of 23</td>
<td>22</td>
<td>45, XX, -7/46, XX</td>
</tr>
</tbody>
</table>

*BL-U, blood unstimulated; BL-S, blood stimulated with PHA; BM, bone marrow; (D) direct preparation; (24) 24-hour culture period; (72) 72-hour culture period.

**Table 2. Acute Nonlymphocytic Leukemia in Patients With Fanconi’s Anemia**

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>Sex</th>
<th>Fanconi’s Anemia</th>
<th>Age at Diagnosis</th>
<th>Chromosome Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMLMld</td>
<td>M</td>
<td>27</td>
<td>27</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>7.5</td>
<td>8</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>F</td>
<td>8</td>
<td>11</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>2</td>
<td>7</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>6</td>
<td>10</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>10</td>
<td>20</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>1.5</td>
<td>3.5</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>F</td>
<td>9</td>
<td>20</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>EL</td>
<td>F</td>
<td>Birth</td>
<td>15</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>EL</td>
<td>M</td>
<td>5.5</td>
<td>15.5</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AMLMld</td>
<td>F</td>
<td>23</td>
<td>28</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>Birth</td>
<td>15</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>Not reported</td>
<td>23</td>
<td>Not reported</td>
<td>Not reported</td>
<td>DR; AZA; C, MTX</td>
</tr>
<tr>
<td>AML</td>
<td>M</td>
<td>14</td>
<td>15</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>ANLL</td>
<td>F</td>
<td>13</td>
<td>26</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>ANLL</td>
<td>F</td>
<td>16</td>
<td>19</td>
<td>Not reported</td>
<td>None</td>
</tr>
</tbody>
</table>

**References**

blasts occurs in patients with Fanconi's anemia. The sisters displayed the expected finding of an increased number of chromosomal breaks prior to the development of ANLL and also developed monosomy 7, as shown by GTG banding (Fig 1) prior to, or coincident with, the development of ANLL.

The significance of deletion of chromosome 7 from the clone of malignant blast cells is unclear. Genes located on chromosome 7 may, in part, regulate leukotaxis. Gahmberg et al have noted a deficiency of GP130, a glycoprotein of neutrophils, in cells from a patient with monosomy 7, which may result in a regulatory defect in myeloproliferation.

Loss of chromosomal material may be found in a percentage of certain malignancies. Classic examples include loss of a portion of the long arm of chromosome 13 (13q−) in retinoblastoma, the 11p deletion in some patients with Wilms' tumor, and the refractory anemia, polycythemia, or preleukemia associated with deletion of the long arm of chromosome 5 (5q−).

Analogous to the loss of chromosomal material in our patients, Meisner, Taher, and Shahidi have reported a similar patient with Fanconi's anemia, who developed erythroleukemia and was found to have a missing C chromosome and probable monosomy 7.

Recently, Chitambar et al have documented the change from a normal karyotype to monosomy 7 in their proband, and group C monosomy in two other family members, each of whom developed ANLL. In that family, 8 of 14 family members in one generation developed fatal aplastic anemia or died with ANLL, but none had phenotypic evidence of Fanconi's anemia.

Chromosomal breakage could predispose to leukemia due to exposure to an environmental agent or accelerated aging due to DNA repair defects. Fibroblasts from these patients show an increased sensitivity to SV 40-induced chromosomal breakage. The development of monosomy 7 in our two patients, and in one other patient with ANLL and Fanconi's anemia, suggests that chromosomal breakage in Fanconi's anemia may result in abnormal replication, crossing over, or deletion, and that monosomy 7 may be one pattern associated with the emergence of a leukemic cell clone in this disorder.

ACKNOWLEDGMENT

The assistance of V. P. Johnson, MD, University of South Dakota, Vermillion, in supplying the initial karyotype in case 1 and of R. F. Thompson, MD, University of South Dakota, Yankton, in supplying relevant clinical data in case 1 is acknowledged with gratitude. The assistance of Elaine Ryan in typing the manuscript and of Genevieve C. Holtz in preparation of the figures is greatly appreciated.

REFERENCES

7. German J: Bloom's syndrome. I Genetical and clinical observa-
Transformation of Fanconi’s anemia to acute nonlymphocytic leukemia associated with emergence of monosomy 7

TJ Stivrins, RB Davis, W Sanger, J Fritz and DT Purtilo