Dysmyelopoietic Syndrome: Sequential Clinical and Cytogenetic Studies

By Rolf A. Streuli, Joseph R. Testa, James W. Vardiman, Uri Mintz, Harvey M. Golomb, and Janet D. Rowley

Clinical and cytogenetic studies were done on 8 patients with dysmyelopoietic syndrome; 6 of these patients had refractory anemia with an excess of blasts (RAEB), and 2 patients had chronic myelomonocytic leukemia (CMML) according to the French-American-British classification. The ages of these 8 patients (3 female and 5 male) ranged from 45 to 70 yr (median, 61.5 yr). Seven of the 8 patients died 3–86 mo (median, 11 mo) after the onset of symptoms of hemorrhage or infections. Cytogenetic studies of bone marrow cells with the Q-banding technique showed clonal karyotypic abnormalities in 7 of the 8 patients (87.5%). Five of the 7 chromosomally abnormal patients had very complex karyotypes; all 7 patients, however, had at least 1 of 4 specific changes: −5 (or 5q−), −7, +8, and +21. Three of the 7 patients with abnormal karyotypes had had some exposure to potential mutagenic/carcinogenic agents. Five of the 7 patients had serial cytogenetic analyses, 4 of which showed evolution of the karyotype to further complexity; in 2 cases, this coincided with the evolution of the disease into acute leukemia. The median survival time of patients whose initial cytogenetic samples showed both normal and abnormal metaphases was more than twice that of patients who had only normal metaphases initially (12 mo versus 4.5 mo).

Acute myeloid leukemia usually has a fulminant course and, if not treated, leads to death in a few weeks. There are patients, however, whose disease runs an indolent course and who survive for several months or even years without being treated with cytotoxic agents. Rheingold et al.1 proposed the term “smoldering leukemia” for this subgroup of leukemias. They described a total of 21 patients,12 all except one of whom were older than 50 yr when the disease began. The survival ranged between 10 and 90 mo, with a median of 16 mo. The diagnostic criteria and clinical features of this disorder have caused some confusion; it has been described as preleukemic acute leukemia,3,4 preleukemia,5 preleukemic state, atypical leukemia,6 smoldering acute leukemia7,8 and subacute myeloid leukemia.9 The French-American-British (FAB) Co-operative Group has used the term dysmyelopoietic syndrome, which encompasses most of these conditions. Included under this broad term is refractory anemia with excess of blasts (RAEB). This designation describes older patients who have an anemia that appears insidiously and who have a hypercellular bone marrow showing abnormalities in all cell lines.12,13 The main feature of RAEB is an increased proportion of myeloblasts and promyelocytes, which may constitute up to 30% of the nucleated cells of the marrow. This disorder probably is the most frequent of the dysmyelopoietic syndromes.14,15 Another type of dysmyelopoietic syndrome is chronic myelomonocytic leukemia (CMML),16,17 also called subacute myelomonocytic leukemia,18,19 which has many similarities to RAEB; the characteristic difference is the increased number of monocytes in the peripheral blood.13

We have observed 8 patients with these disorders during the past 10 yr at the University of Chicago; their clinical course and the associated cytogenetic findings are the subject of this article.

MATERIALS AND METHODS

Six patients with RAEB and two patients with CMML were admitted to the Hematology/Oncology Section of the University of Chicago Hospitals and Clinics between July 1, 1969 and May 31, 1979. Chromosome-banding patterns were obtained from cells of all 8 patients; five patients had chromosome analyses on more than one date. Patient 5 was included in a previously reported series of 90 patients with acute nonlymphocytic leukemia (ANLL) (patient 84 in Golomb et al.2 and in Testa et al.3). A further review of serial bone marrow (BM) aspirates and bone core biopsies, however, resulted in a revision of the diagnosis to RAEB.

The dysmyelopoietic syndrome of each of the eight patients was classified according to the FAB Co-operative Group criteria2,13 after careful review of peripheral blood smears, BM aspirates, and bone core biopsies. In all cases, 500-cell differential counts were performed on Wright-stained marrow aspirates. Additionally, we carried out cytochemical studies on BM aspirates in three cases in order to confirm the cytologic diagnosis. The cytochemical reactions included peroxidase, naphthol-AS-D chloroacetate esterase, alpha-naphthyl acetate esterase with and without NaF inhibition, and the periodic-acid-Schiff (PAS) reaction.

A patient was considered to have evolved to acute leukemia when the sum of myeloblasts and promyelocytes had reached 50% of the BM cells.
CYTOGENETICS IN DYSMYELOPOIETIC SYNDROME

Most of the BM specimens obtained for evaluation of the patient’s clinical status were also examined cytogenetically. Preparation and analysis of metaphases from BM and peripheral blood were performed as previously described. Metaphases were stained and photographed with quinacrine fluorescence to show Q-bands; the same metaphases, stained conventionally with Leishman-Giemsa, were photographed before or, in some cases, after fluorescence. Chromosome identification and karyotypic nomenclature were in accordance with the recommendations of the Paris Conference.

Patients were considered to be cytogenetically abnormal if a clone of abnormal cells was found. If a sample contained a minimum of two hyperdiploid, two pseudodiploid, or three hypodiploid cells showing the same chromosome alteration on banding, this was considered evidence for the existence of an abnormal clone.

The clinical course of each of the eight patients were reviewed carefully. Survival was calculated from the beginning of symptoms as well as from the time of diagnosis.

RESULTS

Cytogenetics

In 7 of the 8 (87.5%) cases, clonal karyotypic abnormalities were present in BM cells from initial cytogenetic samples (Table 1). One patient (4) had an extra no. 8 as the only abnormality. Another patient (7) showed a loss of Y initially, whereas later in the disease course, all abnormal metaphases had a karyotype of 45,XY,−7,+ double minute or 45,XY,−7. The other five patients with initial chromosome abnormalities had very complex karyotypes.

The three most frequent abnormalities were −5, −7, and −20, each being observed in three patients. One patient (6) with a −5 showed this abnormality in a minor clone late in the disease course only; the major abnormal clone in all samples from this patient, however, showed partial loss of the long arm of no. 5 (5q−) as well as other abnormalities.

Five of the patients underwent multiple cytogenetic analyses. Four of the five (3, 5, 6, 7) showed evolution of the karyotype to further complexity during the disease course. The fifth patient did not show any evidence of karyotypic evolution.

In the following four patients, the evolution of the karyotype is compared to the changes in the myeloblast content of the BM.

Table 1. Summary of Cytogenetic Findings in Eight Patients With Dysmyelopoietic Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sample Date</th>
<th>Sample Source*</th>
<th>Total No. of Metaphases†</th>
<th>Percent Abnormal‡</th>
<th>Abnormal Karyotypes§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-14-75</td>
<td>BM</td>
<td>25 (15)</td>
<td>100</td>
<td>44-47,XY,−3,−5,−7,−12,−16,−20,del(1)(q32), 3p−;del(11)(q22)?;+3to6mar,+ring</td>
</tr>
<tr>
<td>2</td>
<td>10-21-75</td>
<td>BM</td>
<td>17 (4)</td>
<td>100</td>
<td>56-64,XY,−2,+6,+9,+13,+15,+19,+21,+10 or 13 mar</td>
</tr>
<tr>
<td>4</td>
<td>7-1-77</td>
<td>BM</td>
<td>23 (13)</td>
<td>85</td>
<td>44,XY,−6,−7,−E;del(3)(p23?);+mar/45,XY,−3,−5,+mar</td>
</tr>
<tr>
<td>5</td>
<td>8-4-77</td>
<td>BM</td>
<td>28 (12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6-2-76</td>
<td>BM</td>
<td>11 (8)</td>
<td>92</td>
<td>Initial &amp;</td>
</tr>
<tr>
<td>7</td>
<td>8-3-76</td>
<td>BM</td>
<td>16 (12)</td>
<td>92</td>
<td>Initial</td>
</tr>
<tr>
<td>8</td>
<td>10-18-76</td>
<td>BM</td>
<td>36 (16)</td>
<td>100</td>
<td>Initial</td>
</tr>
<tr>
<td>9</td>
<td>10-21-76</td>
<td>BM</td>
<td>18 (11)</td>
<td>100</td>
<td>Initial</td>
</tr>
<tr>
<td>10</td>
<td>2-2-77</td>
<td>BM, PB</td>
<td>20 (9)</td>
<td>100</td>
<td>−6,−7,−20/−4,−6,−7,−20; complex (see text)</td>
</tr>
<tr>
<td>11</td>
<td>6-15-77</td>
<td>BM</td>
<td>15 (6)</td>
<td>100</td>
<td>−4,−6,+mar 1,+mar 2,+mar 4; complex (see text)</td>
</tr>
<tr>
<td>12</td>
<td>5-10-74</td>
<td>BM</td>
<td>30 (8)</td>
<td>38</td>
<td>45,XX,−9,−17,−20,del(4)(q21),del(5)(q12?q31?),+der(17), t(9;17)(p13;p11),−cen frag</td>
</tr>
<tr>
<td>13</td>
<td>7-17-74</td>
<td>BM</td>
<td>33 (17)</td>
<td>59</td>
<td>46,initial but +2 cen frag</td>
</tr>
<tr>
<td>14</td>
<td>1-15-75</td>
<td>BM</td>
<td>36 (18)</td>
<td>22</td>
<td>45-47, initial but +1 to 3 cen frag</td>
</tr>
<tr>
<td>15</td>
<td>3-14-75</td>
<td>BM</td>
<td>32 (16)</td>
<td>94</td>
<td>44-48, initial but +0 to 4 cen frag/44,XX,−5,−12,−16,−17,−2 mar</td>
</tr>
<tr>
<td>16</td>
<td>7-8-69</td>
<td>BM</td>
<td>77 (62)?</td>
<td>73?</td>
<td>45,XX,−?Y</td>
</tr>
<tr>
<td>17</td>
<td>12-5-69</td>
<td>BM</td>
<td>79 (45)?</td>
<td>10?</td>
<td>Initial</td>
</tr>
<tr>
<td>18</td>
<td>2-2-70</td>
<td>BM</td>
<td>256 (71)?</td>
<td>8?</td>
<td>Initial</td>
</tr>
<tr>
<td>19</td>
<td>9-14-70</td>
<td>BM</td>
<td>70 (21)?</td>
<td>0?</td>
<td>Initial</td>
</tr>
<tr>
<td>20</td>
<td>6-12-73</td>
<td>BM</td>
<td>55 (19)</td>
<td>95</td>
<td>45,XY,−7,+ double minute/45,XY,−7</td>
</tr>
<tr>
<td>21</td>
<td>9-6-74</td>
<td>BM</td>
<td>34 (13)</td>
<td>100</td>
<td>45,XY,−7,+ double minute/45,XY,−7</td>
</tr>
<tr>
<td>22</td>
<td>1-14-75</td>
<td>BM</td>
<td>23 (19)</td>
<td>100</td>
<td>45,XY,−7,+ double minute/45,XY,−7</td>
</tr>
<tr>
<td>23</td>
<td>3-18-75</td>
<td>BM</td>
<td>11 (6)</td>
<td>95</td>
<td>45,XY,−7,+ double minute/45,XY,−7</td>
</tr>
<tr>
<td>24</td>
<td>3-23-79</td>
<td>BM</td>
<td>28 (15)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*BM, bone marrow; PB, peripheral blood without PHA stimulation.
†Number in parentheses indicates subtotal of informative metaphases examined in detail with fluorescence banding technique, unless marked with ‡, in which case the number in parentheses is the number of conventionally stained metaphases that were photographed and analyzed.
‡Calculated as percentage of informative metaphases examined with fluorescence banding technique unless marked with ††, in which case the figure is the calculated overall percentage of metaphases examined with conventional stain (presence or absence of Y confirmed by fluorescence in some cells).
§When there is more than one abnormal cell line in a sample, the karyotypes are listed in descending order according to size of cell population.
¶"Initial" indicates an abnormal karyotype identical to that seen in the initial sample from a patient.
††These two markers were also seen earlier in a single cell from each of the first two samples from this patient.
Patient 3. The initial sample from this patient showed a hyperdiploid clone (Table I). The second sample from this patient showed two hypodiploid clones, both of these were related to the initial clone, since they were -5 and had a -3, or a partial loss of no. 3 (3p-). Each of the two clones seen in the second sample showed an identical new B-group-size marker. At the time of karyotypic evolution, the percentage of blasts in the BM rose to 50%, and the patient’s disease was considered to have evolved into acute leukemia. A cytogenetic sample obtained 1 mo later, after chemotherapy, was normal, but the BM still contained foci of myeloblasts (Fig. 1).

Patient 5. The chromosomal pattern in this patient was referred to briefly elsewhere (patient 84 in Golomb et al. and in Testa et al.). It was not possible to determine a karyotype for this patient, since the presence of abnormalities showed substantial variability from cell to cell. Briefly, nearly all cells in the initial sample were -6, -7, -20; in addition, -X, -10, -17, and mar 1-mar 3 were present in most cells. Several cells were also -4, indicating that at least two related abnormal clones were present. A second sample showed evidence of karyotypic evolution. All cells were -4, -6, +mar 2, +mar 4. Other abnormalities (i.e. -X, +13, +16, -17, +18, -20, +mar 1, +mar 3) were each found in 2-5 (of 6) analyzed cells, but in varying combinations. The percentage of blasts in the BM remained unchanged throughout the course of the disease, ranging between 10% and 11%.

Patient 6. The karyotypic pattern of some samples from this patient was described earlier (patient 87 in Golomb et al. and in Testa et al.). All four samples from this patient contained a clone which was -9, -20, 4q-, and a 5q- and losses of a no. 9 and a no. 20. One no. 17 has additional brightly fluorescent material on the short arm, which appears to originate from part of the short arm of the missing no. 9. The abnormalities are on the left in each chromosome pair.

Patient 7. The first sample from this patient showed a -Y in 73% of the metaphases examined. The blast count at that time was only 2%, and the patient’s disease was diagnosed as aplastic anemia. Three BM samples obtained over the next 14 mo showed a consistent decrease in the size of the cell population that contained the -Y. The first four samples (Table I) were described in more detail elsewhere (patient 1 in Rowley). In a BM sample
obtained on June 12, 1973, no \( -Y \) cells were observed. Approximately 63% of the metaphases were \(-7\) and had a dully fluorescent fragment that appeared to be a double minute chromosome. About 32% of the cells had a \(-7\), but had no fragment. At that time, the blast count in the BM had risen to 10% and the number of monocytes in the peripheral smear was elevated; the diagnosis of CMML was now evident. The blast count was approximately 10% throughout the course of the disease.

**Clinical Findings**

The age of the 8 patients with dysmyelopoietic syndrome ranged from 45 to 70 yr, with a median of 61.5 yr (Table 2). There were 3 female and 5 male patients. The most frequent symptoms before the first admission to the hospital were fatigue (6 of 8 patients) and weakness (5 of 8 patients); less frequent were weight loss, easy bruising ability, and anorexia. Only 2 of the 8 patients suffered from bleeding problems and from recurrent infections. The physical examination at admission revealed splenomegaly in 5 of the 8 patients; in 4 of these, only the tip of the spleen was palpable, and in one the spleen reached 4 cm below the left costal margin. Only one patient had slight hepatomegaly. Four patients had petechiae of the skin and two among these also of the mucous membranes. Skin nodules were observed in two patients and enlarged lymph nodes in one.

All but one patient were anemic at the time of their first hospital admission. The hematocrit values of the 8 patients ranged from 19.8 to 39.2 (Table 2), with a median value of 30.1%. The anemia was normocytic and normochromic. Three patients had low and five had normal reticulocyte counts. In five patients, we observed nucleated red blood cells in the peripheral blood. The number of white blood cells ranged from 1.6 to 21.7 \( \times 10^9\) /liter, with a median of 4.8 \( \times 10^9\) /liter. Four patients were leukopenic (white blood cells below 5.0 \( \times 10^9\) /liter), and two patients had leukocytosis on admission (16.9 and 21.7 \( \times 10^9\) /liter, respectively). In five patients, the smears of the peripheral blood showed a small number of myeloblasts ranging from 1% to 9% (Table 3). The differential counts of the two patients with CMML were characterized by an elevated number of monocytes (28% and 33%, respectively), whereas normal numbers of monocytes were found in the remaining six patients. All patients were thrombocytopenic; their platelet counts ranged from 5 to 188 \( \times 10^9\) /liter, with a median value of 26.5 \( \times 10^9\) /liter.

The folate level was measured in the serum of four patients; it was normal in one patient and decreased in three patients. Four of six patients had an elevated vitamin B12 level (Table 2). Leukocyte alkaline phosphatase was measured in five patients; it was low in three and normal in two patients (Table 2). One patient with CMML had an elevated serum muramidase level (Table 2). The second patient, with the same diagnosis, did not excrete an elevated amount of muramidase in the urine. Serum and urine muramidase were also measured in two patients with RAEB and were elevated in both.

The BM of all 8 patients was hypercellular, the cellularity ranging from 70% to 100% (Table 3). The characteristic feature of all bone marrow samples at the time of admission and throughout the course of the disease was an increased number of myeloblasts, ranging from 8% to 21%. The BM examinations showed various abnormalities in all three cell lines, including micromegakaryocytes and megaloblastoid, dysplastic red cell precursors. The maturing white cells were severely dysplastic in most patients (nuclear excrescents, poor granulation, pseudo-Pelger-Huët forms). Several patients showed an increase in the reticulin content of the BM. Auer rods were not visible in any patient during the dysmyelopoietic phase of the disease; they appeared, however, in patients 3 and 6 after transformation of their disease into acute leukemia. In most patients, the dysplastic white cells (pseudo-Pelger-Huët forms) and precursors appeared also in the peripheral blood smears. The platelets were abnormal in several cases.

The median survival time from the onset of symptoms was 11 mo, with a range of 3–86 mo (Table 2). The median survival time from the day of diagnosis was 8 mo, with a range of 0.3–19 mo. One patient with CMML (8) was alive when this report was prepared. Two patients (3 and 6) evolved into ANLL 5 mo and 8 mo respectively, after onset of the symptoms of dysmyelopoietic syndrome. Clinically they were characterized by very low initial leukocyte and platelet counts (mean white blood cell count, 1.9 \( \times 10^9\) /liter versus 9.6 \( \times 10^9\) /liter for the other 6 patients; mean platelet count, 6.5 \( \times 10^9\) /liter versus 74 \( \times 10^9\) /liter for the other 6 patients). Patients 3 and 6 were treated with combination chemotherapy, but did not achieve complete remission. Both died of bleeding complications. The other five patients died of hemorrhage (patients 1, 2, 4, 5) or sepsis (patient 7). In one case (5), terminal gastrointestinal bleeding was preceded by *E. coli* sepsis. Three patients were never treated with cytotoxic drugs during their disease. In three other cases, attempts at chemotherapy with various agents had to be stopped because of severe leukopenia and thrombocytopenia.

The median survival from diagnosis of the four patients (1, 2, 4, 5) whose initial cytogenetic samples
<table>
<thead>
<tr>
<th>Patient</th>
<th>Cyto-</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Hematocrit (%)</th>
<th>White Blood Cells (x 10^3) /Liter</th>
<th>Platelets (x 10^3) /Liter</th>
<th>LAP Score</th>
<th>Vitamin B12 (in 200-600 pg/ml)</th>
<th>Folic Acid (in 3.8-20.0 pg/ml)</th>
<th>Muramidase Serum</th>
<th>Muramidase Urine</th>
<th>Survival From Diagnosis (Months)</th>
<th>Survival From Onset of Symptoms (Months)</th>
<th>Treatment</th>
<th>Evolution</th>
<th>Cause of Death**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RAEB</td>
<td>M</td>
<td>45</td>
<td>26.7</td>
<td>16.9</td>
<td>188</td>
<td>92</td>
<td>1550</td>
<td>3.0</td>
<td>14.0</td>
<td>8.7</td>
<td>None</td>
<td>3</td>
<td>Unchanged</td>
<td>Adrenal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RAEB</td>
<td>M</td>
<td>70</td>
<td>28.7</td>
<td>2.8</td>
<td>28</td>
<td>ND†</td>
<td>800</td>
<td>2.2</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>2</td>
<td>5</td>
<td>Unchanged</td>
<td>CNS bleeding</td>
</tr>
<tr>
<td>3</td>
<td>RAEB</td>
<td>M</td>
<td>48</td>
<td>19.8</td>
<td>1.6</td>
<td>5</td>
<td>ND</td>
<td>440</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>AraC, 6TG, DNR (2 x 3 cycles)</td>
<td>8</td>
<td>8</td>
<td>Unchanged</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>4</td>
<td>RAEB</td>
<td>F</td>
<td>59</td>
<td>32.4</td>
<td>6.4</td>
<td>23</td>
<td>1</td>
<td>1110</td>
<td>2.0</td>
<td>9.0</td>
<td>8.5</td>
<td>Hydroxyurea Busulfen</td>
<td>8</td>
<td>17</td>
<td>Unchanged</td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>RAEB</td>
<td>F</td>
<td>63</td>
<td>32.4</td>
<td>4.5</td>
<td>25</td>
<td>32</td>
<td>1600</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>AraC, 6TG, DNR (5 days)</td>
<td>7</td>
<td>11</td>
<td>Unchanged</td>
<td>GI bleeding and sepsis</td>
</tr>
<tr>
<td>6</td>
<td>RAEB</td>
<td>F</td>
<td>62</td>
<td>31.6</td>
<td>2.1</td>
<td>8</td>
<td>20</td>
<td>200</td>
<td>5.4</td>
<td>ND</td>
<td>ND</td>
<td>AraC, 6TG (5 days)</td>
<td>12</td>
<td>16</td>
<td>AML</td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td>7</td>
<td>CMLL</td>
<td>M</td>
<td>61</td>
<td>27</td>
<td>5.0</td>
<td>52</td>
<td>81</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>6 MP (2 mil)</td>
<td>19</td>
<td>86</td>
<td>Unchanged</td>
<td>Sepsis</td>
</tr>
<tr>
<td>8</td>
<td>CMLL</td>
<td>M</td>
<td>64</td>
<td>39.2</td>
<td>21.7</td>
<td>128</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>20</td>
<td>None</td>
<td>2+</td>
<td>2+</td>
<td>Unchanged</td>
<td></td>
</tr>
</tbody>
</table>

*RAEB, refractory anemia with an excess of blasts; CMLL, chronic myelomonocytic leukemia.
†LAP, leukocyte alkaline phosphatase.
ND, not done.
§-normal range.
AraC, cytarabine arabinoside; 6TG, 6-thioguanine; DNR, daunorubicin; 6MP, 6-mercaptopurine.
AML, acute myelogenous leukemia.
**CNS, central nervous system; GI, gastrointestinal.
showed only abnormal metaphases was 4.5 mo, whereas it was 12 mo for the 3 patients (3, 6, 7) who had both abnormal and normal metaphases in the initial sample. Because of the small number of patients, a statistical analysis of the data was not feasible.

**DISCUSSION**

*Chromosomes: Specific Patterns and Evolution of Karyotype*

Karyotypes are generally normal in bone marrows from hematologically normal controls and from patients with anemias due to iron deficiency or gastrointestinal bleeding (Testa and Rowley, unpublished observation); however, some elderly male adults show loss of a Y chromosome.28 The incidence of clonal karyotypic abnormalities was high (87.5%) in our patients with dysmyelopoietic syndrome compared to the incidence of clonal abnormalities in ANLL, which is approximately 50%.29 Patients with myeloid leukemia in a dysmyelopoietic or subacute phase may have an increased likelihood of having an abnormal and very complex karyotype; however, additional patients must be studied so that this can be evaluated further.

Only a small number of chromosome-banding studies on patients with dysmyelopoietic syndrome have been reported in the literature. Since the definition of this disease has been controversial for a long time, it is difficult to compare these studies; some, however, deal with the same group of patients we have examined, i.e., patients with RAEB and with CMML. The largest series of patients with RAEB was reported by Harousseau et al.30 They studied 15 patients, 5 of whom had karyotypic abnormalities; 4 of these 5 patients developed acute leukemia. Milner et al.31 reported on nine patients with RAEB, three of whom had an abnormal karyotype. In three patients, all with a normal karyotype, the disease eventually evolved into ANLL. In the same report, five patients with CMML were included, of whom three had an abnormal karyotype. No nonrandom chromosomal abnormalities were described in either of the above reports.

In a study of patients with myeloproliferative or cytopenic disorders, Nowell and Finan32 observed clonal karyotypic abnormalities in 6 of 10 patients with refractory anemia and in 13 of 35 patients with...
pancytopenia (excluding those with sideroblastic anemia). Cytogenetic abnormalities were demonstrated with banding techniques in 7 patients with pancytopenia and in one with refractory anemia. Of these 8 patients, one was missing a no. 7 and 3 others were missing a C-group chromosome, which may have been a no. 7; 2 of these 4 patients also showed a loss of all or part of a no. 5. Since the number of myeloblasts in the BM was not indicated, however, it is difficult to compare this series clinically with our patients.

Several abnormalities seen in our patients appear to be nonrandom, particularly −5 or 5q−, −7, and −20. Loss of no. 7 is the second most frequent abnormality seen in ANLL, and a −5 is also common in this disease.33 Gain of a no. 8 is the most frequent finding in ANLL de novo, but was found in only one patient with dysmyelopoietic syndrome (patient 4) in our study.

Losses of nos. 5 and 7 are of particular interest in the light of several recent investigations. In a study of myeloid cells from 10 patients who developed ANLL following treatment for a malignant lymphoma, a loss of no. 5 was seen in at least 8 patients and a loss of no. 7 in 5.34 Further examination of other patients who developed ANLL secondary to treatment for malignant lymphomas, multiple myeloma, cancer of the cervix, or for a renal transplant have confirmed the nonrandom loss of nos. 5 and 7 (Rowley, unpublished observations). The association of prior chemotherapy and radiation therapy, which are potentially mutagenic and carcinogenic, with the etiology of these secondary acute leukemias remains to be determined.

An important question that cannot yet be answered concerns the etiologic factors in ANLL de novo and in dysmyelopoietic syndrome. Mitelman et al.35 recently reported on a retrospective study of 56 patients with ANLL de novo, 23 of whom had a history suggesting occupational exposure to chemical solvents, insecticides, and petroleum products, and 33 of whom had no history of such occupational exposure. Only 24.2% of the nonexposed group had clonal chromosome abnormalities. In contrast, 82.6% of the exposed patients had abnormalities, and 84.2% of these patients had at least 1 of 4 particular changes: −5 (or 5q−), −7 (or 7q−), +8, and +21. In the nonexposed group, only one patient had a −7 and one had a +21; none showed a −5 or a +8. In our series of 8 patients, 3 had had a possible occupational exposure to chemicals (patients 1, 2, and 3, all of whom had worked in steel mills). It may be significant that, like the exposed ANLL patients in the study by Mitelman et al.,35 a high percentage of our patients with dysmyelopoietic syndrome had an abnormal karyotype and that all 7 of these abnormal patients had at least 1 of these same 4 changes (i.e., −5 or 5q−, −7, +8, +21).

Partial loss of chromosome no. 5 (5q−) in BM cells, as was observed in patient 6, has been reported in several patients with RAEB36-39 who appeared to be clinically very similar to our group of patients.

Loss of chromosome no. 20 is uncommon in ANLL de novo or in ANLL secondary to therapy for a previous malignancy. However, partial loss of the long arm (20q−) has been reported in polycythemia vera,40 idiopathic acquired refractory sideroblastic anemia,41 as well as in various other myeloid disorders.42

The incidence of karyotypic evolution was high in our patients with dysmyelopoietic syndrome, being observed in four of the five patients studied serially. We recently reported that karyotypic evolution can be a frequent occurrence in ANLL de novo; of 60 patients who were studied serially, 17 (28%) showed evidence of evolution during their disease.21

Clinical Correlations

Since we had studied several sequential BM specimens in five of our eight patients, we tried to correlate the cytogenetic findings with the evolution of the clinical course and the BM abnormalities.

In two of our patients, the dysmyelopoietic syndrome evolved into an acute leukemia. In patient 3, a change in the karyotype to further abnormality and an increase in the percentage of abnormal metaphases to 85% coincided with the increase of the percentage of myeloblasts in the BM 26 wk prior to death (Fig. 1). In the other patient (6), the transformation into acute leukemia preceded the appearance of a new abnormal clone by 2 mo. In both cases, a change in the karyotype to further abnormality and an increase of the percentage of abnormal metaphases approximately coincided with the transformation of the disease into acute leukemia. However, evolution of the karyotype was not necessarily followed by a clinical change, since patients 5 and 7, who both showed chromosomal evolution, still had a dysmyelopoietic syndrome.

In acute myelogenous leukemia, it has been shown that patients whose metaphases are abnormal have a shorter median survival time (2 mo) than patients with either a mixture of abnormal and normal metaphases (median survival time, 8 mo) or those with only normal metaphases (median survival time, 13 mo).20 In the present study of dysmyelopoietic syndrome, the median survival time of patients with both normal and abnormal metaphases was more than twice as long (12 mo) as that of patients with only abnormal metaphases (4.5 mo) thus tending to support the findings in patients with acute myelogenous leukemia, although the number of patients in the present series is very small.

Our studies confirm the view that the dysmyelo-
poietic syndrome, including RAEB and CMML, is an entity with distinct clinical, morphological, and cytogenetic features.

A striking similarity is evident between the cytogenetic abnormalities in our patients and those found in patients who developed ANLL after treatment for other malignancies as well as in patients who had been exposed to potentially mutagenic/carcinogenic agents. In addition, the clinical and morphological features of dysmyelopoietic syndrome closely resemble those of the early or preleukemic stages of ANLL evolving as a second malignancy. Both entities are characterized by anemia, leukopenia, and thrombocytopenia, with various morphological abnormalities in all three cell lines and an elevated percentage of immature white cell precursors in the BM. These similarities raise the question whether mutagenic substances may also play an etiologic role in dysmyelopoietic syndrome, as was suggested for the above-mentioned subgroups of ANLL. Further epidemiologic, clinical, and cytogenetic studies may provide an answer to this question.

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Dysmyelopoietic syndrome: sequential clinical and cytogenetic studies

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