Chromosome 3 Abnormalities in Acute Nonlymphocytic Leukemia (ANLL) With Abnormal Thrombopoiesis: Report of Three Patients With a "New" Inversion Anomaly and a Further Case of Homologous Translocation

By R. Bernstein, M. R. Pinto, A. Behr, and B. Mendelow

An inversion of chromosome 3q is described for the first time in three patients with ANLL, all of whom showed platelet and megakaryocyte abnormalities. A fourth patient who also had abnormal thrombopoiesis, showed a translocation between the homologues of 3q, similar to two previously documented such cases. This provides further indirect evidence for the role of chromosome 3 in thrombopoiesis.

RESULTS

Hematologic Data

The hematologic data at presentation are summarized in Table 2. A striking feature in all four patients was abnormal large platelet morphology, which was assessed independently of the cytogenetic findings. The platelet count was >600 x 10^9/liter in 2 of 4 patients (D.S. and T.M.) and although not raised in the others, was relatively high for patients presenting with de novo ANLL; in A.R. the platelet count rose to 492 x 10^9/liter, 6 mo after presentation, at a time when his peripheral blood contained 90% blasts. In all 4 cases, bone marrow examination revealed megakaryocytes represented mainly by small, hypolobulated forms (Fig. 1, A and B). Megakaryocyte numbers were assessed as increased overall in patients T.M. and A.R., or focally distributed in patients D.S. and T.B. Three patients were classified as M1-ANLL, and patient T.M. had M2 morphology.

Chromosome Studies

The results of chromosome studies are presented in Table 3. Three patients all showed the same structural abnormality on chromosome 3, which was interpreted as inv(3) (q21q26) or inv(3) (pter → q21:q26 →

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Table 1. Clinical Data on Four Patients With ANLL

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Ethnic Group</th>
<th>Occupation</th>
<th>Bleeding History</th>
<th>Chemotherapy*</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.S.</td>
<td>M</td>
<td>57</td>
<td>W</td>
<td>Bus driver</td>
<td>+</td>
<td>COAP → TAA</td>
<td>1.5</td>
</tr>
<tr>
<td>T.M.</td>
<td>M</td>
<td>41</td>
<td>B</td>
<td>Gold-miner</td>
<td>-</td>
<td>TAA</td>
<td>4</td>
</tr>
<tr>
<td>A.R.</td>
<td>M</td>
<td>67</td>
<td>W</td>
<td>Builder</td>
<td>-</td>
<td>COAP</td>
<td>12</td>
</tr>
<tr>
<td>T.B.</td>
<td>M</td>
<td>23</td>
<td>W</td>
<td>Hotel Manager</td>
<td>+</td>
<td>TAA</td>
<td>4</td>
</tr>
</tbody>
</table>

*TAA, thioguanine, cytosine arabinoside, adriamycin; COAP, cyclophosphamide, vincristine, cytosine arabinoside, prednisone.

There was no detectable structural abnormality of any of the other chromosomes to suggest that the abnormal 3q was due to a translocation from another chromosome (a full representative karyotype of patient A.R. is shown in Fig. 3). Patient D.S. also had a monosomy 7 and showed additional abnormalities in some of the karyotypically abnormal cells, viz, 45, XY, -7, inv(3q)/46, XY, -7, inv(3q), + G-group marker/46, XY, -7, inv(3q), + G mar, t(1;2) (p22;p16). Patient T.B. showed a translocation between the homologues of chromosome 3; the translocation was interpreted as t(q21;q26 → qter) (Fig. 2). There was no detectable structural abnormality of any of the other chromosomes to suggest that the abnormal 3q was due to a translocation from another chromosome (a full representative karyotype of patient A.R. is shown in Fig. 3). Patient D.S. also had a monosomy 7 and showed additional abnormalities in some of the karyotypically abnormal cells, viz, 45, XY, -7, inv(3q)/46, XY, -7, inv(3q), + G-group marker/46, XY, -7, inv(3q), + G mar, t(1;2) (p22;p16). Patient T.B. showed a translocation between the homologues of chromosome 3; the translocation was interpreted as t(q21;q26 → qter), but unfortunately, the quinacrine banding was of such poor quality that it was not possible to establish the exact breakpoints on 3q. Patients D.S., T.M., and T.B. showed only karyotypically abnormal cells in unstimulated cultures (AA), whereas patient A.R. had both normal and abnormal cells (AN). Metaphases with a normal karyotype were found in the PHA-stimulated lymphocytes in all four patients, indicating that the abnormalities observed were not constitutional.

DISCUSSION

Structural aberrations of chromosome 3q have been observed in a variety of malignant conditions, but they differ from those observed by us. The remarkable similarity of the 3q inversion in our three cases, all suffering from ANLL and all showing prominent magakaryocyte and platelet abnormalities, must be considered a nonrandom association not previously encountered. Inversion of chromosome 3 has been reported in a carcinoma of the rectum and a malignant mesothelioma, but these were pericentric with breakpoints differing from one another and from the present cases. A review of chromosomal findings in lymphoma showed a concentration of chromosome 3 abnormalities to regions p21 and q21.

The homologous 3q translocation in patient T.B., who also showed the same characteristic thrombopoietic abnormalities, resembles the two other documented cases. The apparently "balanced" nature of these abnormalities raises the question of a "position" effect in triggering a malignant transformation, as was discussed by Hecht and McCaw.

Two of the three patients with an inv(3q) and both patients with an ins(3q;3q) described by Sweet et al. had a raised platelet count of >600 × 10⁹/liter at presentation, a rare phenomenon in de novo ANLL. Patients A.R. and T.B. did not have a thrombocytosis but did have a higher platelet count than is usually encountered in ANLL. Moreover, as these counts were performed by automated methods, populations of large platelets may have been missed, yielding falsely low results.

The breakpoints common to both the inversion and translocation abnormalities of 3q in these six cases (the present four and those already reported), appear to be 3q21 and 3q25 or q26. Rowley and Potter observed one other patient with ANLL in whom a t(3;5) showed a breakpoint at 3q25; the platelet count in this patient was 240 × 10⁹/liter. Few other cases of ANLL (where breakpoints are recorded) showed abnormalities of 3q; breakpoints at 3q27 are described in two individuals and region 3q21 was involved in another two cases, but abnormalities of platelets and megakaryocytes are not specifically recorded. Regions 3q21 and 3q26 were involved in two cases of chronic myelocytic leukemia (CML).

Table 2. Hematologic Data at Presentation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hb (g/dl)</th>
<th>WCC (x 10⁹/liter)</th>
<th>Percent Blasts</th>
<th>Platelet Count (x 10⁹/liter)</th>
<th>Abnormal Large Platelets</th>
<th>Abnormal Blasts</th>
<th>Abnormal Micromegakaryocytes</th>
<th>FAB Classification</th>
</tr>
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<tbody>
<tr>
<td>D.S.</td>
<td>5.3</td>
<td>56.9</td>
<td>73</td>
<td>611</td>
<td>+</td>
<td>78</td>
<td>+</td>
<td>M1 (Focal)</td>
</tr>
<tr>
<td>T.M.</td>
<td>12.4</td>
<td>47.0</td>
<td>80</td>
<td>628</td>
<td>+</td>
<td>53</td>
<td>+</td>
<td>M2</td>
</tr>
<tr>
<td>A.R.</td>
<td>10.3</td>
<td>8.6</td>
<td>70</td>
<td>140</td>
<td>+</td>
<td>60</td>
<td>+</td>
<td>M1</td>
</tr>
<tr>
<td>T.B.</td>
<td>7.2</td>
<td>151.0</td>
<td>80</td>
<td>129</td>
<td>+</td>
<td>83</td>
<td>+</td>
<td>M1 (Focal)</td>
</tr>
</tbody>
</table>
Fig. 1. (A) Hypolobulated
micromegakaryocytes on mar-
row aspirate film from patient
T.M. May-Grunewald-Giemsa
stain, ×1300. (B) Extensive
micromegakaryocyte infiltra-
tion in marrow trephine section
from patient A.R. Hematoxylin
and eosin stain, ×850.

Table 3. Chromosome Studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Karyotype</th>
<th>No. of Peripheral Blood Metaphases Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>+ PHA</td>
</tr>
<tr>
<td>DS*†</td>
<td>Normal cells</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Abnormal clones</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Clone 1: 45,XY, -7, inv(3)(q21q26)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Clone 2: 46,XY, -7, inv(3)q, + G group marker</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Clone 3: 46,XY, -7, inv(3)q, + G group mar.t(1;2)(p22;p16)</td>
<td>6</td>
</tr>
<tr>
<td>TM*</td>
<td>Normal cells</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Abnormal clone: 46,XY.inv(3)(q21q26)</td>
<td>13</td>
</tr>
<tr>
<td>AR‡</td>
<td>Normal cells</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Abnormal clone: 46,XY.inv(3)(q21q26)</td>
<td>1</td>
</tr>
<tr>
<td>TB*‡</td>
<td>Normal cells</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abnormal clone: 46,XY,t(3;3)(q276;q279)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Chromosome results at presentation.
‡Chromosomes first studied 11 mo after diagnosis.
†Previously reported.
Hypolobulated micromegakaryocytes and morphologically abnormal platelets (with or without a raised platelet count) are not uniquely associated with abnormalities of chromosome 3. They are a characteristic feature of the 5q− syndrome and have also been noted in dysmyelopoietic patients showing abnormalities of other chromosomes or normal karyotypes. It would therefore appear that gene loci on 3q are not solely responsible for normal thrombopoiesis, although a point mutation on 3q (or elsewhere) cannot be excluded in the above instances.

The monosomy 7 that was present in addition to abnormality of 3q in patient D.S. and in the patient investigated by Sweet et al. is not thought to be responsible for the thrombopoietic abnormalities observed; the other patients did not show this monosomy. Loss of chromosome 7 has been observed in a variety of dysmyelopoietic, preleukemic, and leukemic
CHROMOSOME 3 ABNORMALITIES IN ANLL

disorders\(^1\) as well as in "secondary" ANLL following exposure to mutagenic agents.\(^2\)\(^-\)\(^4\)

The associated abnormalities of chromosome 3q and thrombopoiesis were unrelated to the standard FAB classification of ANLL.\(^3\) Two of the three cases with inv(3q) and the patient with t(3;3) had M1 morphology, while the third patient with an inv(3q) had M2 morphology. The previously reported patients had myelomonocytic leukemia\(^1\) (= M4-ANLL) and acute myeloblastic leukemia.\(^2\) The FAB classification of ANLL is based on morphology and distribution of granulocyte, monocyte, and erythroid precursors, but does not consider associated abnormalities of megakaryocytes and their precursors. The chromosome 3q abnormalities discussed in this report may therefore assist in identifying a specific subgroup of ANLL (M7) analogous to the t(15;17) chromosome abnormality specifically associated with M3-ANLL and the t(8;21) found only in M2-ANLL.\(^5\)

The three patients (D.S., T.M., and T.B.) who survived less than 4 mo all showed only karyotypically abnormal myeloid cells, whereas patient A.R. had both chromosomally normal and abnormal cells, which could be one of the reasons for his longer survival of 12 mo.\(^6\)

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REFERENCES

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