A Pericentric Inversion of Chromosome 16 Is Associated With Dysplastic Marrow Eosinophils in Acute Myelomonocytic Leukemia

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Cytogenetic studies were performed in 18 consecutive children with acute nonlymphoblastic leukemia (ANLL) between 1981 and 1983. Three children with acute myelomonocytic leukemia (AMMoL; M4, FAB classification) had the following unique bone marrow morphology and cytogenetic abnormality: eosinophilic precursors with dysplastic violaceous granules and a pericentric inversion of chromosome 16. Surface marker analysis of leukemic cells from these patients, using a panel of monoclonal antibodies, revealed the expression of a series of monocyte markers. The association of an inversion of chromosome 16 with abnormal eosinophil morphology in the M4 subtype of ANLL appears to represent a unique subgroup of patients.

RESULTS

All 18 children had an adequate number of metaphases for cytogenetic analysis, and of these, 15 were found to have a clonal chromosome abnormality as defined by the Second International Workshop.2 Among those patients with chromosome abnormalities were 3 patients where the sole chromosome abnormality was the presence of a pericentric inversion of chromosome 16 at diagnosis. The breakpoints were placed at p13 and q22, respectively, from Q-banded karyotypes. The inversion rendered this chromosome to appear metacentric (Fig. 1). In patient no. 1, 3/28 metaphases were chromosomally normal at diagnosis, as were 1/26 in patient no. 2 and 8/32 in patient no. 3. Follow-up cytogenetic studies of bone marrow in remission showed the disappearance of the inversion 16 clone in all the patients (Fig. 2).

Physical examination of the 3 patients revealed enlarged nodes, palpable spleens (2 of 3), and bruises...
PERICENTRIC INVERSION OF CHROMOSOME 16

Fig. 1. Karyotype prepared from a Q-banded metaphase from patient 3 at diagnosis. Arrow points to chromosome 16 with a pericentric inversion. The karyotype is: 46,XY, inv(16)(p13q22). The missing chromosome 22 is a random loss from this metaphase.

Fig. 2. Karyotype prepared from a Q-banded metaphase from patient 3 at remission. The karyotype is: 46,XY. Notice both copies of chromosome 16 are normal.

Fig. 3. Bone marrow film from patient 3, showing eosinophilic precursors with dysplastic violaceous granules.

or petechiae (2 of 3). The clinical features of the patients are summarized in Table 1.

All patients had morphology and histochemistry (myeloperoxidase, specific and nonspecific esterase positivity) consistent with the diagnosis of acute myelomonocytic (M4) leukemia. The unique bone marrow finding seen in all three patients was the presence of eosinophilic precursors with large violaceous granules in addition to the normal eosinophilic granules (Fig. 3). Normal eosinophils and precursors were also observed in all three marrow specimens. Eosinophilia was not prominent in the peripheral blood (Table 1).

Surface marker analysis showed that cells from two of the three patients expressed Ia, MY4, MY7, MY8, and MY9, whereas cells from the third patient were tested only for Ia and MY9, which were both positive. Greater than 90% of the cells from each patient were reactive with each antibody.

Two of the three patients achieved remission and remain in continuous complete remission.

DISCUSSION

Cytogenetic analysis of leukemic cells in patients with ANLL demonstrated the presence of consistent clonal chromosome abnormalities in about 50% of the cases.5,12 However, with the application of cell culture and synchronization methods,13-15 yielding better quality of chromosome preparations and allowing a more detailed analysis, the frequency of ANLL cases with clonal abnormalities is steadily increasing.16

Recently, Arthur and Bloomfield8 reported a partial deletion of the long arm of chromosome 16, [del(16)(q22)] in 5/61 cases of ANLL studied by

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Hb (g/dl)</th>
<th>WBC (x 10^3/liter)</th>
<th>Platelets (x 10^3/liter)</th>
<th>Percent Eosinophils</th>
<th>Percent Blasts</th>
<th>Bone Marrow</th>
<th>FAB</th>
<th>Response</th>
<th>Survival in Months From Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) S.K.</td>
<td>M</td>
<td>12/12</td>
<td>9.4</td>
<td>39</td>
<td>181</td>
<td>1</td>
<td>40</td>
<td>11</td>
<td>6</td>
<td>M4</td>
<td>PR</td>
</tr>
<tr>
<td>(2) M.P.</td>
<td>M</td>
<td>11</td>
<td>11.5</td>
<td>95</td>
<td>165</td>
<td>2</td>
<td>58</td>
<td>15</td>
<td>6</td>
<td>M4</td>
<td>CR</td>
</tr>
<tr>
<td>(3) T.E.</td>
<td>M</td>
<td>12</td>
<td>12.7</td>
<td>52</td>
<td>127</td>
<td>4</td>
<td>59</td>
<td>12</td>
<td>10</td>
<td>M4</td>
<td>CR</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; WBC, white blood cell count; CR, complete remission; PR, partial remission.
them. The breakpoint was identified at q22 from Giemsa-banded karyotypes. Three of their patients were classified as M2, and the other two as M4 leukemia. However, in the addendum, they noted that, in the absence of special stains, some of the hematologists at the Fourth International Workshop felt that all five cases could be considered as M4. The unique pretreatment clinical finding in all patients was the presence of bone marrow eosinophilia with abnormal granules.

Among 308 patients with ANLL, LeBeau et al. observed an inversion or both an inversion and deletion of chromosome 16 in 18 AMMoL (M4) patients. In 8 of their patients, the only abnormality was inversion 16. The remaining 10 had other clonal chromosome abnormalities. Both copies of chromosome 16 were abnormal in some of the clones from 3 patients. One of the copies had a deletion [del(16)(q22)] and the other an inversion [inv(16)(p13q22)]. All 18 patients had distinctly abnormal eosinophil morphology and ultrastructure.

The breakpoints in the abnormal chromosome 16 [inv(16)(p13q22)] in the 3 AMMoL patients studied by us are similar to those reported by LeBeau et al. Our patients also had similar morphological abnormalities in marrow eosinophilic precursors. A single case of AMMoL with an inversion 16 with similar breakpoints has been reported. However, the bone marrow eosinophil morphology was not commented on. The bone marrow morphology of our patients closely resembled a single case of "eosinophil-myoelomonocytic leukemia" reported by Stavem et al. No clonal cytogenetic abnormality was found in their patient. The predominant surface antigen phenotype of our patients (Ia, MY4, MY7, MY8, and MY9) is highly correlated with AMMoL and AMoL morphology. In particular, the expression of monocyte-restricted antigen MY4 is characteristic of AMMoL. This subgroup of ANLL patients with abnormalities of chromosome 16, M4 morphology, and abnormal eosinophils may constitute a discrete group.

**ADDENDUM**

Patient no. 3 had a central nervous system, and subsequently bone marrow, relapse after 6 mo in remission. (Added in proof.)

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**REFERENCES**

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