A 20q DELETION ORIGINATING IN A PLURIPOTENT STEM CELL

To the Editor:

Cytogenetic deletions involving human chromosome 20q are typically associated with myeloid disorders such as polycythemia rubra vera (PRV)\(^1\) and refractory anemia,\(^2\) both of which occasionally terminate as acute myeloid leukemia (AML). These deletions are thought to be interstitial with a proximal breakpoint in band 20q11.2 and distal breakpoints in bands 20q13.1 and q13.3 for the smaller and larger deletions, respectively.\(^3\)

We report cytogenetic and cell culture studies involving a 37-year-old male patient with Philadelphia chromosome positive (Ph-positive) acute lymphoblastic leukemia (ALL) whose disease was characterized by two nonrandom cytogenetic abnormalities, a t(9;22)(q34;q11) identifying the leukemic clone at diagnosis of ALL, and a 20q deletion associated with disease remission. Clonal cytogenetic abnormalities are rarely observed after successful remission induction of patients with acute leukemia when the bone marrow (BM) is usually repopulated by cells of normal karyotype.

When ALL (French-American-British [FAB] L2) was diagnosed in April 1984, 7 of 20 unstimulated BM metaphases showed the abnormal karyotype 54.XY, +2, +4, +5, +17, −19, inv(1), t(9;22)(q34;q11), Ph, +3C, +Bmar. The other 13 metaphases showed a normal male karyotype. At that time there was no organ enlargement or basophilia to suggest presentation at lymphoid blast crisis of chronic myeloid leukemia (CML). After treatment appropriate for a lymphoid disease (induction with vincristine, prednisone, Adriamycin, and L-asparaginase; consolidation with VM26 and cytosine-arabinoside), complete remission was achieved in August 1984 when two of five BM metaphases showed a 20q deletion as the sole cytogenetic abnormality. The deletion persisted throughout a 2.5-year BM remission maintained with oral methotrexate and 6-mercaptopurine. During that time it was detected in some CFU-GM, BFUe, and CFU-GEMM colonies, and in 5 of 36 B-lymphoblastoid cell lines (B-LCLs) resulting from the Epstein-Barr virus (EBV) immortalization of remission mononuclear cells (Table 1). As shown in Fig 1, the deletion appeared to be interstitial with breakpoints in chromosome bands q11.2 and q13.1. The presence of the 20q deletion in both myeloid and lymphoid lineages provided strong circumstantial evidence that it originated in a pluripotent stem cell. The Ph translocation on the other hand was not seen in myeloid colonies during disease remission, suggesting that it was lineage restricted.

Table 1. Cytogenetic Analysis of Remission Cells by Direct Methods, After Clonal Culture in Methylcellulose (CFU-GM, BFUe, and CFU-GEMM colonies), and of Epstein-Barr Virus-Transformed B-LCLs Derived From Remission Samples

<table>
<thead>
<tr>
<th>Source of Metaphases</th>
<th>Metaphases With Normal Karyotype</th>
<th>Metaphases With 20q Deletion</th>
<th>Total Metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct and short-term cultures</td>
<td>70</td>
<td>42</td>
<td>112</td>
</tr>
<tr>
<td>CFU-GM</td>
<td>87</td>
<td>36</td>
<td>123</td>
</tr>
<tr>
<td>BFUe</td>
<td>19</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>CFU-GEMM</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>B-LCLs</td>
<td>31*</td>
<td>5*</td>
<td>36</td>
</tr>
</tbody>
</table>

These results are pooled aggregates from five BM samples spanning the period of disease remission.

* Number of independently derived B-lymphoblastoid cell lines with a normal karyotype or a 20q deletion as the sole cytogenetic abnormality.

Metaphases with the 20q deletion never displaced those with a normal karyotype during disease remission, suggesting that the deletion did not impart a significant proliferative advantage to the stem cell in which it arose. Nor did it affect this cells ability to differentiate normally as evidenced by the size, cell composition, and cytochemical staining properties of CFU-GEMM, BFUe, and CFU-GM colonies with the 20q deletion that were indistinguishable from those of normal karyotype. Progenitor cell assays performed during disease remission showed in vitro growth patterns comparable with those of a normal BM.

The significance of cytogenetically unrelated clones in leukemic patients remains unclear. As the 20q deletion was not present in the leukemic clone at diagnosis of ALL, it was unlikely to have contributed to the initiation or progression of our patient's disease. The deletion may have resulted from genetic instability in a premalignant stem cell whose progeny were not detected at diagnosis because they were at a proliferative disadvantage relative to cells with the Ph translocation. Alternatively, it could have signified the early stages of an underlying myeloid disorder more commonly associated with 20q deletions. Yet another possibility is that the deletion may have

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been treatment induced as proposed for the acquired cytogenetic abnormalities observed in the BM of patients with PRV after treatment with 32P alone or in combination with cytotoxic drugs. Of the many nonrandom cytogenetic abnormalities characterizing subtypes of myelodysplasia and AML, only the t(9;22) of CML has been shown to originate in a pluripotent stem cell. Whether or not this is true for all Ph-positive diseases including ALL and AML has yet to be resolved. The cellular origins of these recurring cytogenetic abnormalities have important therapeutic implications. Thus, the only potentially curative treatment for hematologic diseases arising in a pluripotent stem cell is allogeneic BM transplantation (BMT). Furthermore, the persistence of clonal cytogenetic abnormalities during disease remission of acute leukemia raises doubts about the efficacy of autologous BMT if there is inadequate cytogenetic or molecular evaluation of the sample before infusion.

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A 20q deletion originating in a pluripotent stem cell [letter]

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