Four New Recurring Translocations in Non-Hodgkin Lymphoma

By Ellis G. Levine, Diane C. Arthur, Joy Machnicki, Glaucio Frizzera, David Hurd, Bruce Peterson, Kazimiera J. Gaj-Peczalska, and Clara D. Bloomfield

The identification of recurring chromosomal translocations has provided clues to the gene regions important in lymphoma development. Among 157 patients with non-Hodgkin lymphoma studied by cytogenetic analysis, four new recurring translocations have been identified—t(8;9) (q24;p13), t(11;18)(q21;q21), t(14;15)(q32;q15), and an unbalanced translocation giving rise to der(22)t(17;22) (q11;p11). Each translocation appeared twice. The t(11;18) was the only karyotypic abnormality in the two patients with it, and the t(14;15) was the sole karyotypic abnormality in one patient. All translocations were found in B-cell malignancies and were associated with both nodal and extranodal disease. Among the regions affected, only the immunoglobulin heavy-chain gene MYC, and BCL2, have thus far been associated with lymphoma. The breakpoint sites identified by these translocations warrant further investigation at the molecular level.

RECURRENT TRANSLOCATIONS have been of particular interest in the non-Hodgkin lymphomas (NHL), as the microscopical translocation of chromosomal material has identified events of biologic significance. For example, t(8;14)(q24;q32) results in the deregulation of the MYC gene,1 and the molecular characterization of the 11q13 breakpoint of t(1;14)(q13;q32) and the 18q21 breakpoint of t(14;18)(q32;q21) has led to the identification of the putative oncogenes BCL1 and BCL2, respectively.2-3 In this report we present four new recurring translocations in NHL and some of their biologic and clinical associations, and discuss their potential significance.

MATERIALS AND METHODS

This report derives from the successful cytogenetic examination of 157 cases of NHL. After informed consent was obtained, cytogenetic analysis was performed in involved lymph nodes or other tumor masses from consecutive patients referred to the University of Minnesota. In all instances, the same tumor mass was simultaneously studied for histologic subtype, immunologic phenotype, and G-banded chromosomes. The portion of the tumor examined histologically was fixed in B5. Histologic classification was performed in all instances, the same tumor mass was simultaneously studied for histologic subtype, immunologic phenotype, and G-banded chromosomes. The portion of the tumor examined histologically was fixed in B5. Histologic classification was performed in each patient without knowledge of the chromosome findings by one of us (GF) using the International Working Formulation for Clinical Usage.4 Our immunologic methods have been previously described.5 Among the surface antigens studied, listed according to their CD designation,6-8 active-synchronized short-term (24- and 48-hour) unstimulated cultures, using methods previously described.7 G-banding was performed according to the Wright technique of Sanchez et al.8 Photographs of metaphases were taken on high-contrast film, and multiple photokaryotypes were constructed in each case. Karyotypes were designated according to the International System for Human Cytogenetic Nomenclature (1985).9 Chromosome abnormalities were defined as clonal if two or more metaphase cells had identical structural abnormalities or extra chromosomes, or if three or more metaphase cells had identical missing chromosomes.

RESULTS

t(8;9)(q24;p13) (Fig 1A). This translocation was identified in two patients, one of whom was untreated (Table 1). In the treated patient (S34), a follicular, small cleaved-cell lymphoma and a follicular mixed lymphoma had been diagnosed 11 and 2 years, respectively, prior to his only cytogenetic analysis (Table 2), at which time a diffuse, mixed small and large cell lymphoma was diagnosed. Both patients had extranodal involvement. Although the karyotypes of both of these patients were complex, the only other abnormality common to them was the t(14;18).

t(11;18)(q21;q21) (Fig 1B). The two patients with this translocation were similar in many ways: both had small lymphocytic lymphomas, both were previously untreated, both had extranodal involvement, both had $μ$ monoclonal proliferations, and both had this abnormality as their only structural aberration.

t(14;15)(q32;q15) (Fig 1C). This translocation was identified in two patients, one of whom was untreated. The treated patient (S37) had been diagnosed with a small noncleaved-cell lymphoma and had the same histology at progression four months later. The karyotype at progression had two clones; one contained the t(14;15) alone. The second clone, although unrelated to the first, was related to a clone found at diagnosis. On the other hand, the t(14;15) did not appear in the karyotype obtained at diagnosis (Table 2). Both patients had extranodal disease.

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DISCUSSION

Recurring translocations have been of special interest in the malignant lymphomas, as their breakpoints have been instrumental in delineating areas of the genome important to lymphomagenesis, either by implicating a previously mapped oncogene (eg, MYC) or by suggesting the presence of putative oncogenes (eg, BCL1 and BCL2). The Ninth Human Gene Mapping Workshop identified 17 recurring translocations in NHL, four of which were newly reported by us in abstract form at that conference. This report details the cytogenetic, histologic, immunophenotypic, and clinical information relative to these four translocations. Notably, only one of the four involved the 14q32 band; therefore, several new genomic regions of potential importance are suggested.

The t(8;9)(q24;p13) was found in two patients, both with diffuse B-cell histologies. Visceral disease was present in both cases. Of interest, Pollak and Hagemeijer noted that all four B-cell NHL patients in their series with alterations of 9p12-21 (all deletions) also had visceral involvement. A similar translocation, t(8;9)(q24;p21), has been identified in a patient with lymphoblastic lymphoma. The karyotypes of the two patients in our series with a t(8;9)(q24;p13) also contained a t(14;18)(q32;q21); one patient had been originally diagnosed with a follicular lymphoma; the other had a diffuse histology at presentation, but a follicular pattern could not be excluded because no lymph node was studied. Recently, an NRAS-like gene has been mapped to the 9p13 band. The 8q24 band contains the MYC gene.

The two patients with the t(11;18)(q21;q21) were similar in a number of ways. Each had a small lymphocytic lymphoma, a B lymphophenotype, and extranodal involvement. In addition, the translocation was the only abnormality found in both karyotypes. In NHL, the long arm of chromosome 11 is involved in structural alterations in 10% to 15% of cases; the 11q23-25 region is most frequently rearranged, however.

The t(11;14) often associated with small lymphocytic lym-

![Fig 1. Partial G-banded karyotypes showing (A) the t(8;9)(q24;p13) from Patient S33, (B) the t(11;18)(q21;q21) from Patient S35, (C) the t(14;15)(q32;q15) from Patient S36, and (D) the der(22)t(17;22)(q11;p11) from Patient S38.

Table 1. Clinical Characteristics of Patients at the Time of the Identified Translocation

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Age/Sex</th>
<th>IF†</th>
<th>Site of Biopsy</th>
<th>Prior Therapy</th>
<th>Clinical Stage</th>
<th>Extranodal Sites</th>
<th>Treatment‡</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;9)q24;p13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S33</td>
<td>67/M</td>
<td>§</td>
<td>Sinus</td>
<td>No</td>
<td>IVA</td>
<td>Sinus</td>
<td>M,P,A,C,E</td>
<td>21</td>
</tr>
<tr>
<td>S34</td>
<td>57/M (46)</td>
<td>F (B)</td>
<td>Lung</td>
<td>Yes</td>
<td>IVA</td>
<td>Lung</td>
<td>A,V,P</td>
<td>6 (138)</td>
</tr>
<tr>
<td>t(11;18)q21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>56/M</td>
<td>A</td>
<td>Lateral gland</td>
<td>No</td>
<td>IVA</td>
<td>Lateral gland</td>
<td>CHOP-Bleo</td>
<td>78+</td>
</tr>
<tr>
<td>S35</td>
<td>54/F</td>
<td>A</td>
<td>Stomach</td>
<td>No</td>
<td>II A</td>
<td>Stomach</td>
<td>RT</td>
<td>38+</td>
</tr>
<tr>
<td>t(14;15)q32;q15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S36</td>
<td>83/F</td>
<td>A</td>
<td>Orbit</td>
<td>No</td>
<td>IVA</td>
<td>Orbit</td>
<td>Chl</td>
<td>24</td>
</tr>
<tr>
<td>S37</td>
<td>3/M (3)</td>
<td>J (J)</td>
<td>Liver</td>
<td>Yes</td>
<td>IVB</td>
<td>Liver, kidney</td>
<td>AM</td>
<td>0.5 (4)</td>
</tr>
<tr>
<td>der(22)t(17;22)(q11:p11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S38</td>
<td>69/F</td>
<td>A</td>
<td>LN</td>
<td>No</td>
<td>IVA</td>
<td>Liver</td>
<td>None</td>
<td>23+</td>
</tr>
<tr>
<td>S39</td>
<td>51/M (46)</td>
<td>B (G)</td>
<td>LN</td>
<td>Yes</td>
<td>IVA</td>
<td>Liver</td>
<td>C-MOPP</td>
<td>33 (96)</td>
</tr>
</tbody>
</table>

For previously treated patients, data from diagnosis are shown within parentheses.

*Patients S33 through 39 have not been previously reported. Patient S1 has appeared under the same designation in reference 29.

†Histology by the International Working Formulation for Clinical Usage: A, ML, small lymphocytic; B, ML, follicular, predominantly small cleaved cell; F, ML, diffuse, small and large cell; G, ML, diffuse, large cell; J, ML, small noncleaved cell.

‡Initial treatment following the identification of the translocation. Abbreviations: M, methotrexate; P, prednisone; A, Adriamycin (doxorubicin hydrochloride, Adria Labs, Dublin, OH); C, cyclophosphamide; E, etoposide; V, vincristine; CHOP-Bleo, cyclophosphamide, Adriamycin, vincristine, prednisone, bleomycin; RT, radiation therapy; Chl, chlorambucil; LN, lymph node; C-MOPP, cyclophosphamide, vincristine, prednisone, procarbazine.

§Histology was ML, diffuse, but subtype could not be determined.
Table 2. Four New Recurring Translocations Among 157 Patients With Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Surface lg</th>
<th>Cluster of Differentiation No.</th>
<th>No. of Metaphases Studied</th>
<th>Total</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Karyotype of Abnormal Clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>S33</td>
<td>γκ</td>
<td>− + − + + +</td>
<td>17</td>
<td>1</td>
<td>16</td>
<td></td>
<td>48,XY,−1,−15,t(8;9)(q24;p13),t(14;18)(q32;q21),+der(11)(q12),t(7;18)(q21;?),+der(15)q11qter→11q13;1q42→1q21;: 15p11→15qter,+2r</td>
</tr>
<tr>
<td>S34</td>
<td>μλ</td>
<td>ND − − ND ND +</td>
<td>30</td>
<td>13</td>
<td>8</td>
<td></td>
<td>48,X,−Y,−Y,−18,−22,del(2)(p11),del(6)(q273q275),del(7)(p15),t(8;9)(q24;p13),t(12;19)(p11;q13),t(14;18)(q32;q21),+der(8)(8)(q721;?),+der(18)(14;18)(q32;q21),+der(18)(18;7)(q23;?),+der(22)(12;7)(q13;?)</td>
</tr>
<tr>
<td>S35</td>
<td>εμ</td>
<td>− − − − ND ND −</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td></td>
<td>46,XY,t(11;18)(q21;q21)</td>
</tr>
<tr>
<td>S36</td>
<td>μλ</td>
<td>+ + − + + +</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td></td>
<td>50,XX,−X,−X,−6,del(7)(q22q32),+del(7)(q171q17),+der(8)(q11q13),+der(8)(q71q92),t(14;18)(q32;q1),+der(22)(12;2)(q11;?)</td>
</tr>
<tr>
<td>S37</td>
<td>μκ</td>
<td>− + − + + +</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td></td>
<td>46,XY,t(14;15)(q32;q15)</td>
</tr>
<tr>
<td>S38</td>
<td>μλ</td>
<td>+ + + + + +</td>
<td>21</td>
<td>7</td>
<td>14</td>
<td></td>
<td>48,X,−X,−X,−6,−17,−17,−20,−20,−20,−20,del(1)(p22p34),(t11;14)(q13;q23),+2der(20)(t6;20)(p21q13),+2der(22)(17;22)(q11p11),+3mar</td>
</tr>
<tr>
<td>S39</td>
<td>δμλ</td>
<td>− − − − ND ND +</td>
<td>30</td>
<td>6</td>
<td>9</td>
<td></td>
<td>50,XY,−X,−Y,−17,−22,del(6p),t(14;18)(q32;q21),+der(22)(17;22)(q11p11),+3mar</td>
</tr>
</tbody>
</table>

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phoma/chronic lymphocytic leukemia involves the 11q arm, but the breakpoint is in band 11q13.13 No candidate gene for lymphomagenesis has been mapped to 11q21. The YES14 and BCL2 genes are located at 18q21; the latter is being intensely studied.15,17

On the other hand, the two patients with the t(14;15)(q32;q15) were more striking for their dissimilarities. There was a wide disparity in their ages; one had an indolent lymphoma and the other a high-grade lymphoma; one had this translocation as a sole karyotypic abnormality, and the other had a complex karyotype that included this translocation. However, both had B-cell malignancies and each had visceral involvement. A similar translocation—t(14;15)(q32;q21-22)—has been reported in a diffuse large cell lymphoma.18 Although Chevenix-Trench et al.19 found that 10% of NHL patients had a break in the 15q15 band, lymphomagenesis has presently been mapped to 11q21.12 More recently, in a patient with an aggressive B-cell lymphoma, a region of 17q involved in MYC activation has been identified.24,25 However, its location was at band 17q22. Oncogenes located at the 17q11 region include ERBA1 and ERBB2.25,26 No gene implicated in lymphoma has been mapped to 22p11.

In summary, we have identified four new recurring translocations in NHL. Among the genomic regions affected, only the immunoglobulin heavy-chain gene MYC, and BCL2, have been implicated in lymphoma. The breakpoint sites identified by these translocations warrant further investigation at the molecular level. Finally, as molecular studies have identified translocations in tumors in which the cytogenetic abnormality is inapparent,27,28 the low frequency of recurring translocations in this study may belie their importance.

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REFERENCES


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