Chromosome Abnormalities in Poorly Differentiated Lymphocytic Lymphoma

Shirou Fukuhara, Janet D. Rowley, Daina Variakojis, and Harvey M. Golomb

ABSTRACT

Thirteen patients with malignant lymphoma, poorly differentiated lymphocytic type, were studied with cytogenetic and/or immunological techniques. Chromosomally abnormal cells were observed in every case. Immunological studies were done on seven patients who derived cell surface markers and were classified as "null" cell type. Therefore, markers (i.e., "null" cell type) may be related to increasing aneuploidy.

INTRODUCTION

The classification of non-Hodgkin's lymphomas remains a controversial issue, for the individual groups as defined by Rappaport et al. (32) may be heterogeneous (1, 17, 19, 27). Recently, translocations that involve the long arm of chromosome 14 (14q+) have been observed frequently in cells from patients with various kinds of lymphoid cancers (7–11, 13, 21, 22, 28, 30, 31, 41, 42). In a recent study, Fukuhara et al. (10) presented data showing a correlation, in ML-H, between particular chromosome patterns and the histopathology classified according to the recommendation of Lukes and Collins (19).

Thirteen patients with a diagnosis of ML-PDL, have been studied with banding techniques as reported in 3 series (6, 8, 33). The histopathology was not described in detail, however, and the frequency of a 14q+ marker differed among these 3 series.

In the present report, we describe the karyotypes seen in 10 patients with ML-PDL, and we relate specific chromosome changes to the histopathology according to the Lukes and Collins classification (19) and to cell surface markers.

MATERIALS AND METHODS

Cytogenetic Studies

A specimen suitable for chromosome analysis was obtained from 10 of 19 patients with ML-PDL. In 7 patients, the cells were from lymph nodes; cells were obtained from peripheral blood or bone marrow of 3 other patients who were in the leukemic phase.

Chromosomes were prepared as previously described in detail (8), and the analysis was performed with the use of sequential photography of conventional Giemsa and quinacrine (Q−) banding (2) on the same metaphase. In one patient (Case 13), a combination of the Q− with the reverse (R−) banding technique (40) was used for the complete analysis. In another patient (Case 12), the Giemsa (C−) banding technique was also used for staining of heterochromatin (39). Duplicate photographs of the chromosomes stained by each technique were used for identification according to the Paris nomenclature (29). The abnormality was considered clonal when at least 2 cells from a given patient had a similar chromosomal rearrangement or when 3 cells were lacking the same chromosome.

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4 Operated by the University of Chicago for the United States Department of Energy under Contract EY-76-C-02-0069.
5 The abbreviations used are: ML-H, malignant lymphoma, histiocytic type; ML-PDL, malignant lymphoma, poorly differentiated lymphocytic; slg, surface immunoglobulin; E-rosette, erythrocyte-forming rosette; PHA, phytohemagglutinin; B-cells, bone marrow-derived lymphoid cells; T-cells, thymus-derived lymphoid cells.

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Histopathology

A histological diagnosis based on the classification proposed by Rappaport et al. (32) in 1956 was made on the lymph node biopsies in 12 patients and on a bone core biopsy in one patient (Tables 1 and 2); the same lymph node was used for the cytogenetic study. All of these specimens were further classified, according to the criteria of Lukes and Collins (19), as lymphomas composed of cells that were large or small, with either cleaved or noncleaved nuclei; this classification was carried out without knowledge of the results of the cytogenetic studies.

Immunological Studies

$slg$. For the immunoglobulin studies, $5 \times 10^6$ cells collected from peripheral blood of 7 patients who were in the leukemic phase were incubated for 30 min at room temperature with 100 μl of a 1:4 dilution of fluorescein-conjugated $\operatorname{IgA}$, $\operatorname{IgG}$, $\operatorname{IgM}$, $\operatorname{IgK}$, $\operatorname{IgA}$, or polyvalent goat anti-human antiserum (Meloy Laboratories, Springfield, Va.). The antiserum was filtered through a 0.22-nm filter immediately before use for removal of any aggregates. The cells were washed 3 times with Hank's balanced salt solution and then examined with UV illumination in an American Optical fluorescence microscope. For 6 patients (Cases 1, 8, 9, and 11 to 13), a resynthesis study was performed. An aliquot of $10^6$ cells was centrifuged, resuspended in 15 ml of Roswell Park Memorial Institute Medium 1640 containing 15% fetal calf serum (Grand Island Biological Co., Grand Island, N. Y.) and antibiotics, and incubated at $37^\circ$ in a moist 5% CO$_2$ atmosphere for 48 hr. After testing for viability by the trypan blue exclusion method, an aliquot of $5 \times 10^6$ cells was tested for slg as described above. For one patient (Case 8), only polyvalent goat antiserum was used initially and at 48 hr.

**E-Rosette Formation.** An aliquot of $5 \times 10^6$ cells was suspended in 0.4 ml of absorbed fetal calf serum and 0.4 ml of 0.5% washed sheep RBC in 0.01 M phosphate-0.15 M NaCl. The aliquot was incubated at $37^\circ$ for 30 min, spun into a pellet, and put on ice for 2 hr. Next, the cells were resuspended by gentle rolling of the tube, and the percentage of rosette-forming cells was calculated. Only cells with 3 or more adherent erythrocytes were counted as rosette-forming cells.

### RESULTS

The pertinent clinical and pathological data for 13 of the 19 patients with ML-PDL (Cases 1 to 13) are shown in Tables 1 and 2. The detailed chromosomal findings for 10 of the patients are given in Table 3. The remaining 6 patients had no mitotic cells in the biopsied lymph node and were excluded from the study. Seven patients with ML-PDL (Cases 1 to 7) had fewer dividing cells in their lymph nodes than did patients with ML-H (8); the chromosomes were fuzzy and indistinct, with a poorer banding pattern. Cytogenetic studies were also performed on 6 other patients who were in the leukemic phase. Two of these patients (Cases 12 and 13) had a large number of mitotic cells in bone marrow and in cultures of unstimulated peripheral blood, respectively; 3 patients (Cases 8 to 10) had very few cells, and they were also excluded from the study since detailed chromosome analysis was impossible. The remaining patient

### Table 1

**Pertinent clinical and pathological data for 7 patients with ML-PDL**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age (yr)</th>
<th>Therapy</th>
<th>Survival period (mos.)</th>
<th>Rappaport</th>
<th>Lukes and Collins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/57</td>
<td>CC</td>
<td>46</td>
<td>D</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>2</td>
<td>F/55</td>
<td>CC</td>
<td>48</td>
<td>N</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>3</td>
<td>M/53</td>
<td>CC</td>
<td>112</td>
<td>N</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>4</td>
<td>M/90</td>
<td>CC</td>
<td>44</td>
<td>N</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>5</td>
<td>M/55</td>
<td>CC</td>
<td>54</td>
<td>N</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>6</td>
<td>M/48</td>
<td>CC</td>
<td>11</td>
<td>N</td>
<td>SC (+ + +)</td>
</tr>
<tr>
<td>7</td>
<td>F/62</td>
<td>RT + CC</td>
<td>9</td>
<td>D</td>
<td>SN (+ + +)</td>
</tr>
</tbody>
</table>

- These cases correspond to Cases 12 to 18 in Ref. 8.
- CC, combination chemotherapy; RT, radiation therapy.
- D, diffuse; SC, small cleaved cell; N, nodular; SN, small noncleaved cell; LN, large noncleaved cell; +, 5 to 30%; ++, 50 to 100%.
- The diagnosis was made in tonsillar biopsy.

### Table 2

**Leukemic phase of ML-PDL with pertinent clinical, pathological, and immunological data in 7 patients**

The cells from 4 of the 6 patients with ML-PDL, small cleaved-cell type, and one patient with the small noncleaved-cell type are of B-cell origin. Cells from 2 patients with the small cleaved-cell type are classified as null.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age (yr)</th>
<th>Therapy</th>
<th>Survival period (mos.)</th>
<th>Rappaport</th>
<th>Lukes and Collins</th>
<th>WBC/cu mm in peripheral blood</th>
<th>E-rosettes (% positive)</th>
<th>Polyvalent goat antiserum (% stained)</th>
<th>Immunological cell type (type of slg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/57</td>
<td>CC</td>
<td>46</td>
<td>D</td>
<td>SC (+ + +)</td>
<td>22,400 (45)</td>
<td>10</td>
<td>100</td>
<td>B (Mx)</td>
</tr>
<tr>
<td>8</td>
<td>M/71</td>
<td>CC</td>
<td>48</td>
<td>N</td>
<td>SC (+ + +)</td>
<td>28,800 (83)</td>
<td>7</td>
<td>100</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>M/35</td>
<td>RT + CC</td>
<td>45</td>
<td>N</td>
<td>SC (+ + +)</td>
<td>19,000 (&gt;90)</td>
<td>13</td>
<td>40</td>
<td>B (Mx)</td>
</tr>
<tr>
<td>10</td>
<td>M/17</td>
<td>CC</td>
<td>6</td>
<td>N</td>
<td>SC (+ + +)</td>
<td>27,900 (70)</td>
<td>5</td>
<td>0</td>
<td>Null</td>
</tr>
<tr>
<td>11</td>
<td>F/72</td>
<td>ND</td>
<td>60</td>
<td>*</td>
<td>SC (+ + +), SN (+)</td>
<td>6,600 (10)</td>
<td>1</td>
<td>65</td>
<td>B (MA)</td>
</tr>
<tr>
<td>12</td>
<td>M/55</td>
<td>CC</td>
<td>27</td>
<td>D</td>
<td>SN (+ + +), SC (+)</td>
<td>806,000 (&gt;95)</td>
<td>1</td>
<td>100</td>
<td>B (Mx)</td>
</tr>
<tr>
<td>13</td>
<td>M/56</td>
<td>RT + CC</td>
<td>26</td>
<td>N</td>
<td>SC (+ + +), LC (+)</td>
<td>25,400 (70)</td>
<td>4</td>
<td>6</td>
<td>Null</td>
</tr>
</tbody>
</table>

- One patient (Case 8) had an accidental death; other patients died in the natural course, except for Cases 1 and 9 who are still alive.
- A resynthesis study was done in 6 patients (Cases 1, 8, 9, and 11 to 13).
- CC, combination chemotherapy; D, diffuse; SC, small cleaved cell; N, nodular; RT, radiation therapy; ND, not done; SN, small noncleaved cell; LC, large cleaved cell; LN, large noncleaved cell; +, 5 to 30%; ++, 50 to 100%.
- Numbers in parentheses, percentage of abnormal cells.
- The diagnosis was made in the bone marrow biopsy.
- Case 13 is Case 9 in Ref. 8.

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### Table 3

**Cytogenetic findings of cells from tissues primarily involved by ML-PDL in 9 patients and from a PHA-stimulated peripheral blood culture in one patient**

Nine of these 10 patients had a 14q+ marker chromosome. A 14q translocation with 18q leading to the 14q+ marker was found in 4 patients, one of whom had a second 14q translocation with 8q, and was probably present in 2 others. In one patient, each of 2 cells from PHA-stimulated peripheral blood also had a 14q+ marker as well as a Dq+ marker. A 14q translocation with 11q was found in one patient.

<table>
<thead>
<tr>
<th>Case</th>
<th>Source</th>
<th>Therapy before sampling</th>
<th>No. of abnormal cells</th>
<th>Modal chromosome no.</th>
<th>No. of rearranged chromosomes</th>
<th>% of abnormal cells with 14q+ marker</th>
<th>Karyotype</th>
<th>Donor chromosome of 14q+ marker</th>
<th>Marker</th>
<th>Fig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>T</td>
<td>-</td>
<td>5 (7)</td>
<td>48</td>
<td>&gt;6</td>
<td>100</td>
<td>?</td>
<td>48,XY,-C,-14,14q+21q+?+4mar</td>
<td>1, size of No. 3; 3, F size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BM</td>
<td>+</td>
<td>8 (18), 10 (12)</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>18q?</td>
<td>45,XX,-Y</td>
<td>1, like 20</td>
<td>2, A and B, Lines a</td>
</tr>
<tr>
<td>2a</td>
<td>LN</td>
<td>-</td>
<td>6 (6)</td>
<td>48</td>
<td>&gt;5</td>
<td>100</td>
<td>18q?</td>
<td>48,XX,1p+12q+14q+,+18q-7,1mar</td>
<td>2, C size and E size</td>
<td>2, A and B, Lines b</td>
</tr>
<tr>
<td></td>
<td>BM</td>
<td>-</td>
<td>1 (18)</td>
<td>47</td>
<td>4</td>
<td>0</td>
<td>47,XX,-7,8q,-7a,-2mar (1 cell)</td>
<td>1, size of No. 1, C size</td>
<td>2, A and B, Lines b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LN</td>
<td>+</td>
<td>4 (9)</td>
<td>48/50</td>
<td>7</td>
<td>100</td>
<td>18q</td>
<td>48,XY,-6,-11,12+1p-3q,14;18q(32);q21, +2mar</td>
<td>1, size of No. 3; 1, C size</td>
<td>2, A and B, Lines b</td>
</tr>
<tr>
<td>4</td>
<td>LN</td>
<td>+</td>
<td>10 (10)</td>
<td>47</td>
<td>7</td>
<td>100</td>
<td>18q</td>
<td>47,XY,-9,-10,12,-16,(8;13)(p11;q34),(14;18)(q32;q21),+3mar</td>
<td>M1, like del(10q24); M2, part of 18; M3, F size</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>LN</td>
<td>+</td>
<td>6 (6)</td>
<td>46</td>
<td>6</td>
<td>100</td>
<td>18q?</td>
<td>46,XY,-1,-22,del(10q24),17p+14q+,+18q(18q21), +2mar</td>
<td>1, size of No. 3; 1, C size</td>
<td>2, A and B, Lines b</td>
</tr>
<tr>
<td>6</td>
<td>LN</td>
<td>-</td>
<td>2 (4)</td>
<td>45/46</td>
<td>3</td>
<td>100</td>
<td>18q</td>
<td>46,XY,-2,5(1 cell),45,XY,+2,-5,-6,14(14;18)(q32;q21),+mar(1 cell)</td>
<td>1, like 11p</td>
<td>2, A and B, Lines b</td>
</tr>
<tr>
<td>7a</td>
<td>LN</td>
<td>-</td>
<td>2</td>
<td>42,44</td>
<td>4</td>
<td>100</td>
<td>11q</td>
<td>44,XX,-3,-9,-13,-14,-18,+11;14;18q(13;32), +1p+, +2mar</td>
<td>1, like del(1;1p)11? 1, E size</td>
<td>2A, Line d; 2B, Line c</td>
</tr>
<tr>
<td>11a</td>
<td>PB (+PHA)</td>
<td>-</td>
<td>2 (13)</td>
<td>45/46</td>
<td>1-2</td>
<td>100</td>
<td>Dq?</td>
<td>45,XX,-Xq,Dq,Dq-45,XX,14q+</td>
<td>1, like del(1)Xp11? 1, E size</td>
<td>2B, Line d</td>
</tr>
<tr>
<td></td>
<td>BM</td>
<td>0 (13)</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16q</td>
<td>46,XY</td>
<td>M1 &amp; 2, F size M3, der t(14q)</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>BM</td>
<td>+</td>
<td>15 (16)</td>
<td>44</td>
<td>13</td>
<td>0</td>
<td>'</td>
<td>44,XX,-Y,-9,-10,-11,+12,-14,-17,14(14;13.3p5+del(6KXq13),del(8p21), 9G+6p, 19(p+len), 22q+1,-3mar</td>
<td>M1 &amp; 2, F size M3, der t(14q)</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>PB</td>
<td>+</td>
<td>20 (20)</td>
<td>53</td>
<td>20</td>
<td>100</td>
<td>8q,18q</td>
<td>53,XX,-Y,+19,+20KXq11;13KXp15;11;17qXp21;13p13, 1G+4q+del(5KXq13),del(6KXq21), 2G+7q+4q+del(8q24;32),14KXq32;18q(21), 10q+11q+del(11q11), +13p+ +4mar</td>
<td>M1, C size; M2 &amp; M3, E size; M4, ring?</td>
<td>4</td>
</tr>
</tbody>
</table>

* a in Cases 1, 2, and 11, complete banding analysis was impossible, and triploid and tetraploid cells in Case 7 were not studied with banding.

* b Y, t, missing; BM, bone marrow; LN, lymph node; PB, peripheral blood.

* c Number in parentheses, total number of cells studied with banding analysis.

* d Chromosome analysis was done twice, with an interval of 1 year.

* e PB without PHA had no mitoses.

* f Translocation of No. 14 to No. 1 [(1;14)Xp21;q13)].
(Case 11) showed a moderate number of mitoses only in the PHA-stimulated peripheral blood.

Prior to the chromosome studies, 5 patients had received chemotherapy (Cases 3 to 5 and 12) or radiation therapy (Case 13). The other 5 patients (Cases 1, 2, 6, 7, and 11) were not treated with cytotoxic agents or radiation therapy prior to the initial analysis; one patient (Case 1), however, had already received chemotherapy when the bone marrow analyses were done.

Chromosomally abnormal cells were observed in all 9 patients (Cases 1 to 7, 12, and 13) in whom lymphoma tissue could be studied, namely, 7 lymph nodes including a tonsil, one unstimulated peripheral blood, and one bone marrow sample containing leukemic cells; a consistent clonal abnormality could be detected. In one other patient (Case 11), only 2 of 13 cells could be analyzed from a PHA-stimulated culture of peripheral blood were abnormal, and only one of these could be analyzed with banding. This patient is excluded from the discussion of clonal abnormalities. The modal chromosome number in the lymph node cells was pseudodiploid in one case (Case 5), 47 in one (Case 4), and 48 in 3 (Cases 1 to 3); in Case 6, 2 cells had 45 and 46 chromosomes, respectively. In contrast, the seventh patient (Case 7) had 2 different populations consisting of hypodiploid and near-triploid cells. The modal number in the leukemic cells was 43 in one patient (Case 12) and 53 in another (Case 13); cells from these 2 patients showed highly complex chromosome rearrangements.

Although most of these 9 patients had a very complex karyotype with many rearranged chromosomes, all had an abnormality of chromosome 14; in 8 patients this was a 14q+ marker. In 6 patients (Cases 1 to 5 and 13) whose tumor was composed predominantly of small cleaved cells, the marker was present in all abnormal cells; whereas in one patient (Case 6), it was present in one of 2 abnormal cells. A 14q+ marker was identified in the 2 hypodiploid cells from a lymph node of Case 7; the karyotype of the polyplid cells could not be determined. A 14q anomaly different from the 14q+ marker was seen in all of the leukemic cells in Case 12. On the other hand, the tenth patient (Case 11), from whom dividing cells were obtained only in a PHA-stimulated peripheral blood culture, also had 2 abnormal cells, one with a 14q+ marker and one with a Dq+ marker. Although it is uncertain whether these cells are related to the lymphoma, the bone marrow biopsy at this time showed ML-PDL, small cleaved cell type.

The origin of the translocation to the long arm of No. 14 was identified in 6 of these 10 patients and was tentatively identified in 2 others. A 14q+ marker chromosome in 3 patients (Cases 3, 4, and 6) and one of two 14q+ markers in one patient (Case 13) appeared to result from a 14q translocation with 18q [t(14;18)(q32; q21)]. In addition, a t(14;18) was compatible with the banding pattern of the 14q+ chromosome in Cases 2 and 5. Although the size of the 14q+ marker in Case 1 was similar to that of the above 14q+ marker, its origin could not be determined because of the poor quality of banding. The second 14q translocation in Case 13 involved 8q [t(8;14)(q24;q32)]. The banding pattern of the 14q+ marker in Case 6 suggests that the marker could have originated from a 14q translocation with 11q [t(11;14)(q13; q32)], although a normal pair of No. 11’s was present. The identification of a 14q+ marker (one cell) was impossible; a Dq+ marker in the same case (Case 11) might have been the result of a tandem D,D long-arm translocation. One No. 14 in Case 12 could have been translocated to the short arm of one No. 1 [t(1;14)(p21; q13)]; this was the only abnormality of No. 14 that did not yield a 14q+ marker.

Other chromosome abnormalities were noted as well; however, with a few exceptions, these were not the same in different patients. Thus, No. 1 was involved in structural rearrangements in 6 patients; loss of No. 11 or structural rearrangements of the long arm were noted in 5 patients. A loss of one No. 9 or a gain of one No. 12 were each seen in 3 patients. Loss of all of No. 6 was seen in 2 patients, and a deletion of the long arm was noted in 3 others. Nine of the patients had one to 4 marker chromosomes of uncertain origin.

At the time of this study, these 13 patients were in pathologic Stage IV. When the Lukes and Collins classification was used, the lymphoma tissue in 9 patients (Cases 1 to 6 and 8 to 10) had primarily small cleaved cells (Fig. 1A); in 2 patients (Cases 7 and 12), the tissue was composed of small noncleaved cells (Fig. 1B). One patient (Case 11) had a diagnosis of ML-PDL in the bone marrow biopsy, which showed large clusters of small cleaved cells together with a few small noncleaved and large cleaved cells. In the remaining patient (Case 13), the lymph node contained approximately 80% small cleaved cells and 20% large cleaved cells; this patient had a previous diagnosis of malignant lymphoma, mixed cell type (6). A 14q+ chromosome was seen in at least a few cells from every patient with small cleaved cell lymphoma and in one of 2 with the small noncleaved cell type.

The findings in immunological studies on 7 patients (Cases 1 and 8 to 13) who were in the leukemic phase are shown in Table 2. Four of the 6 patients with ML-PDL, small cleaved cell type (Cases 1, 8, 9, and 11), had slg on the leukemic cells, confirming their B-cell origin. Three of these patients had monoclonal slg, IgM in Cases 1 and 9, and IgM in Case 11. The type of slg in the other patient (Case 8) was not studied. Most cells from 2 patients (Cases 10 and 12) had neither slg nor E-rosette formation; they were classified as null. One patient with the small noncleaved cell type (Case 12) had monoclonal IgM on the leukemic cells, which were classified as B.

In 3 cases (Cases 1, 12, and 13) of 7 patients on whom immunological studies were performed, the result was compared with the cytogenetic findings. In the 2 patients whose lymphoma cells were classified as B, lymph node cells of Case 1 had a 14q+ marker, whereas the leukemic cells of Case 12 lacked this marker. On the other hand, leukemic cells in the remaining patient (Case 13) were classified as null and had the most complex rearrangements of chromosomes seen in this group of patients, including two 14q+ markers.

DISCUSSION

The observations made in this study indicate that malignant tissue examined from all 9 patients with ML-PDL had a clone of chromosomally abnormal cells which contained translocations involving chromosome 14. A 14q+ marker was seen in 8 of these patients. Although this marker was derived from different chromosomes, involvement of No. 18 occurred most often. Thus, in 4 patients (Cases 3, 4, 6, and 13), the donor chromosome was No. 18, and it may have been the donor in 2 others (Cases 2 and 5). A second 14q+ chromosome in one

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of these patients (Case 13) was the result of a translocation from 8q. The translocation could be determined in one other patient, in whom it involved 11q.

Chromosome analysis with the use of the G-banding technique has been reported in 13 patients with a diagnosis of ML-PDL (6, 8, 33). The frequency of a 14q+ marker was low compared with that in the present study. In these earlier reports, the marker had been observed in lymph nodes from 5 of 9 patients, in leukemic peripheral blood from one of 3 patients (one of whom had a normal karyotype), and in the pleural effusion of one patient. The discrepancy may be due to the poor quality of the chromosomes obtained from these lymphomas. In one case studied by Reeves (33), some cells had either a 14q+ marker or an 18q-,del(18)(q21); only one cell of 6 that were fully analyzed contained both abnormal chromosomes. Prior to the use of banding techniques, an abnormal chromosome resembling a No. 18 with a deletion in the long arm had been observed in 10 cases of non-Burkitt’s lymphoma, of which 8 had lymphoma suggestive of follicular-center-cell origin (26, 33, 38); identification of a translocation of the small deleted part of the chromosome would have been impossible without banding techniques. In 2 cases (6), a 14q translocation occurred with 11q[t(11;14)(q13;32)]; in one case (8), a tandem 14;14 long-arm translocation was observed. Thus, although not previously recognized, a translocation between the long arm of Nos. 14 and 18 may be a rather frequent event in ML-PDL.

A 14q+ marker chromosome, although found in all abnormal cells of the lymph node, was not seen in bone marrow cells of 2 patients (Cases 1 and 2), which contained foci showing involvement with small cleaved cell lymphoma. Kataki and Sandberg (15) reported that chromosome changes in bone marrow from patients with non-Hodgkin’s lymphoma did not include a 14q+ marker or any other consistent abnormality. These findings indicate that the cytogenetic analysis of lymphoma cells must be done either on lymph node cells or on unstimulated peripheral blood cells during the leukemic phase if the results are to be relevant to the study of lymphoma. It may be that lymphoma cells do not have the same proliferative advantage in the microenvironment of the bone marrow as in the lymph node.

Immunological studies were performed on the leukemic cells of 7 patients (Table 2); the cells from 5 of these patients were classified as B and those from the other 2 as null. The lymphoma of the 2 patients with null cells was of the small cleaved cell type, which is generally accepted to be of B-cell origin. None of the patients had more than 13% of cells that formed E-rosettes (normal, 59 to 77%). Two of 3 patients for whom the cytogenetic findings were compared had B-cell markers with an IgMx clone. In Case 1, the dividing abnormal cells from the lymph node had a 14q+ marker; in the other patient (Case 12) with a small noncleaved cell lymphoma, all of the dividing leukemic cells lacked a 14q+ marker chromosome and had a t(1;14) instead. Lymphoma cells from the third patient (Case 13) were classified as null; all of his dividing leukemic cells had 2 different 14q+ marker chromosomes and the most complex rearrangement of chromosomes in this series. Catovsky et al. (3) have reported chromosome and immunological studies performed on ascitic fluid cells from one patient, who was classified on the basis of lymph node biopsy as having follicular lymphoma. Almost all of his cells had slg, and the dividing cells showed the presence of one or 2 different 14q+ markers. Thus, in these 4 patients, 3 of whom had a 14q+ marker, 2 had B-cell markers and one (Case 13) lacked them. One other patient lacked a 14q+ marker, although he had a monoclonal slg. This lack of a clear correlation between the cytogenetic and immunological studies may reflect a change in the biological function of these cells. The cells may lose the capacity to express B-cell markers in the leukemic phase; thus, the data may not exclude the B-cell origin of these leukemic cells. The loss of differentiated function of these cells (the secretion of slg in Case 13) may be related to the increasing aneuploidy and to the complexity of the karyotype noted in the leukemic cells as compared with cells from the lymph nodes.

Recently, 7 patients with ML-H have been reported (11); a 14q+ marker chromosome was present in most of the abnormal cells obtained from 3 of these patients whose tumors were composed predominantly of large noncleaved cells. The marker was absent in all of the abnormal cells from the 4 patients whose tumors were composed of a majority of large cleaved cells. Thus, a 14q+ marker chromosome has frequently been observed in at least 3 types of follicular-center-cell lymphomas as defined by Lukes and Collins (19), namely, large noncleaved cell, small cleaved cell, and small noncleaved cell lymphomas. Among small noncleaved follicular-center-cell lymphomas, which include Burkitt’s lymphoma, Burkitt’s lymphoma has a consistent 14q translocation with 8q (14q+ marker) t(8;14)(q24;q32) (24, 43), whereas others may have other 14q translocations, as observed in Cases 7 and 12. Our data are too limited, however, to provide more than suggestive evidence on this point.

In the myeloproliferative disorders, the study of chromosome changes, especially translocations, has revealed a close correlation between a specific translocation and a particular type of leukemia. Examples are the 9;22 translocation in chronic myeloid leukemia (35), the 8;21 translocation in acute myeloblastic leukemia (34, 37), and the 15;17 translocation in acute promyelocytic leukemia (36). The frequent occurrence of abnormalities of 14q in lymphoid disorders strongly suggests that rearrangements of 14q provide these cells with a proliferative advantage (8, 25). A particular 14q translocation might be preferentially associated with a specific disorder. Thus, an 8;14 translocation has been seen consistently in Burkitt’s lymphoma (24, 43), and a tandem 14;14 translocation occurs frequently in ataxia telangiectasia (12, 25). Our observations suggest that a 14;18 translocation may be common in ML-PDL, small cleaved cell type. An 11;14 translocation has also been noted in several patients with ML-PDL. These translocations have occasionally been seen in various other types of lymphoid cancers, including ML-H, which has a variable pattern of 14q translocations (4, 8, 18, 23, 43).

On the other hand, a 14q translocation is not specific only for follicular-center-cell lymphoma of B-cell origin. The translocation has also been observed in some lymphoid cancers which are of T-cell origin, namely, one case of mycosis fungoides (9), 2 cases of chronic T-cell leukemia (5), one T-cell line derived from acute lymphoblastic leukemia (14), and a clone of PHA-stimulated lymphocytes in telangiectasia (12, 25), a primary immunodeficiency disease which predisposes to lymphoid cancer (16). The question is thus whether the precise translocation constitutes a critical change in a particular lymphoid cell, which may then have a variety of different
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appearances, or whether a particular type of lymphoid disorder (based on morphology) may have various types of translocations. The resolution of this question will clearly provide a significant advance in our understanding of the biology of these cells and will therefore permit us to establish a reasonable system of classification of the lymphoproliferative disorders.

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REFERENCES

Fig. 3. Q-band karyotype of a cell from Case 4. The abnormal chromosome is on the left in each pair. Note the deletion of 8p and 18q; addition of 13q and 14q; absence of one No. 9, one No. 10, and one No. 16; trisomy for No. 12; and 3 unknown markers (M1, M2, and M3). M1 might be a deletion of 10q24, and M2 might contain part of the missing No. 6. The 13q+ chromosome and the 14q+ chromosome each could be the result of a translocation with 8p and 18q, [(t(8;13)(p11;q24))] and [(t(14;18)(q32;q21)], respectively.
Fig. 4. R-banding karyotype of a cell in Case 13. There is an extra X and No. 20 and loss of the Y. Note the deletion of 1q (left), 1p (center), 2q, 5q (left), 6q, 8q, 11q (right), and 16q; addition of 4q, 5p (right), 10q, 11q (left), 13p, and two 14q+; a gain of the abnormal No. 7 (7q+); and 4 unknown markers (M1 to M4). The 1q− chromosome originates from a translocation with 5p [(t(1;5)(q11;p15)], and the 1p− chromosome could be the result of a translocation with No. 17 [(t(1;17)(q21;p13)]. The two 14q+ chromosomes could be the result of a 14q translocation with 6q and 19q [(t(6;14)(q24;p32)] and [(t(14;19)(q22;q21)], respectively. The 5q− and the 6q− chromosome each could have an interstitial deletion of the long arm, [del(5)(q13q31)] and [del(6)(q21q23)], respectively. The 11q− chromosome has lost the whole long arm. M4 could be a ring chromosome.
Fig. 5. Q-banding karyotype of a variant cell (+ No. 12) in Case 12. Note the deletion of 6q, 8q, and 19p or q; addition of 1p, 5p, 11q, 13q, 17p, and 22q; absence of one No. 9, one No. 10, one No. 14, one No. 17, one No. 21, and the Y chromosome; and 3 unknown markers (M1, M2, and M3). One No. 9 with a deletion of q has an addition of unknown origin at the end of p. The 1p+ chromosome could be the result of a translocation with 14q [t(1;14)(p22;q13)], and M3 might be the remaining part of one No. 14 involved in the translocation. The addition of 11q (11q+) could originate from one No. 21 [t(11;21)(q23;q22)].
Chromosome Abnormalities in Poorly Differentiated Lymphocytic Lymphoma

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