Cytogenetic Studies and Clinical Aspects of Patients with Plasma Cell Leukemia and Leukemic Macroglobulinemia

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ABSTRACT

Chromosomes of six patients with plasma cell leukemia and one patient with leukemic macroglobulinemia were examined from peripheral blood, bone marrow, and/or pleural fluid. All the patients had a clonal chromosomal abnormality. The modal chromosome number was near tetraploid in two, pseudodiploid in two, and hypodiploid in three patients. Rearrangements of chromosome 1 were found in all the patients. The most consistent abnormality was a large marker involving the long arm of No. 1, found in six patients, including the patient with macroglobulinemia. Each patient had one to four large markers which resulted in partial trisomy to hexasomy for the long arm of No. 1. The translocations occurred with No. 9 in two, with No. 16 in two, and Nos. 8, 17, and 18 each in one patient. The survival time from the diagnosis was less than 1 year in five of them and over 2 years in one. The only patient whose cells lacked an extra 1q lived for over 3 years. Five 14q+ marker chromosomes were detected in three patients. The donor chromosome was No. 11 in one of these and was undetermined in the others; the size of each 14q+ marker seemed quite different which suggested different donor chromosomes. Loss of a sex chromosome was found in five patients. Loss of No. 13 and gain of No. 7 or 7q were each found in two patients. Rearrangement or deletion of the short arm of No. 8 was found in five patients. A rearrangement of 9p was found in three patients. The myeloma cells had a different morphology in the peripheral blood, bone marrow, and/or pleural fluid before and after the leukemic phase of one patient; however, chromosome analysis revealed the same clone despite the altered morphology.

INTRODUCTION

PCL is an infrequent phase in MM. The clinical course may be fulminant with features resembling those of acute leukemia, and it is sometimes recognized as a distinct subentity (28). Chromosome studies in patients with MM and related paraproteinemic disorders have often been reported (1, 3, 10, 11, 15, 16, 22, 23, 26, 29), but there are few reports of PCL (8, 11, 16, 26). In MM, the pattern of chromosome aberrations has been quite variable, and no consistent markers were noted in the published data. On the other hand, it has been suggested that the 14q+ marker may be necessary for the leukemic evolution of myeloma cells (16). This assumption remains tentative because of lack of data in PCL.

We report the chromosome studies and the clinical and morphological features in 6 patients with PCL and in one patient with leukemic MG. The karyotypic differences between these patients and reported cases of leukemias, malignant lymphomas, and MM are discussed.

MATERIALS AND METHODS

Chromosomes of 6 patients with PCL and one patient with leukemic MG were examined from peripheral blood, bone marrow, and/or pleural effusion specimens. PCL was defined as more than 0.5 x 10^9 circulating plasma cells or plasmoblasts per liter. The peripheral blood mononuclear cells were separated with Ficoll-sodium metrizoate gradient centrifugation and were cultured in Roswell Park Memorial Institute Medium 1640 containing 10% fetal calf serum at 37°C for 24 to 48 hr in 5% CO2. Bone marrow and pleural fluid samples were processed directly without prior culture. Mitotic cells were arrested with 1 x 10^-6 M colchicine for 2 hr, treated with 0.075 M KCl for 10 to 30 min, and subsequently fixed in methanol:acetic acid (3:1). Air-dried slides were first stained with Giemsa and then photographed; after destaining, the same cells were restained with quinacrine mustard and photographed with a fluorescence microscope. Case 1 was banded with a G-banding method (21). Descriptions of the chromosomes follow the recommendations of the ISCN (1978) (9).

RESULTS

Clinical data on the 7 patients are presented in Table 1. Four patients had PCL at the time of initial diagnosis, and in 2 patients (Cases 1 and 5) a leukemic phase subsequently developed. The patient with MG (Case 7) also had leukemic plasmacytoid cells at diagnosis. The survival after diagnosis was less than 1 year in 5 patients and over 2 years in 2. All the patients had anemia, hypercalcemia, and renal insufficiency. Three had hepatosplenomegaly (Cases 1, 2, and 5), and 3 (Cases 2, 5, and 6) had pleural effusion with plasma cell invasion. In addition, one had progressive lower limb paresis (Case 2), one had meningeal involvement (Case 5), and another had obstructive jaundice with plasma cell invasion (Case 6). Postmortem examination in 3 patients (Cases 1, 2, and 5) showed very extensive infiltration of the marrow, liver, lymph nodes, lungs, and other organs with plasma cells.

Cytogenetic data are presented in Table 2. Chromosomes were studied before treatment in 2 patients, after treatment in 4 patients, and before and after treatment in one patient. There were no clear differences between the karyotypes of untreated patients and those of treated patients. All of the patients had a clonal chromosomal abnormality. In 2 patients (Cases 1 and 2), the cells from bone marrow, peripheral blood, and/or pleural effusion had the same karyotype. In another patient...
A rearrangement of the short arm of No. 8 was found in 4 patients, and an 8p- chromosome was found in one. The break point in 8p was near the centromere in 3 patients, p12 in one and p23 in the other patient. A rearrangement of the short arm of No. 9 was found in 3 patients and a rearrangement of the long arm of No. 9 was found in one patient. The break point of 9p was p23 in one patient, p24 in the second, and undetermined in the third. Two patients with near tetraploid chromosome numbers each had 2 extra No. 7 chromosomes or 7qchromosomes: segment q21-qter, in addition to the tetraploidy. Five patients showed loss of a sex chromosome; there was loss of an X in one female and one male and loss of a Y in 3 males. A loss of No. 13 and a loss of No. 22 was each found in 2 patients.

**CASE REPORTS**

**Case 1.** The clinical and immunological findings of Patient M. Y., a 45-year-old man, were already reported (24). Cyto-

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### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Serum protein</th>
<th>WBC in peripheral blood (×10^9/liter)</th>
<th>% of plasma cells and atypical lymphocytes in peripheral blood</th>
<th>Therapy before chromosome examination</th>
<th>Total duration of disease (mos.)</th>
<th>Survival after chromosome examination (mos.)</th>
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<tbody>
<tr>
<td>1 (M. Y.)</td>
<td>M</td>
<td>45</td>
<td>Absent</td>
<td>52.1</td>
<td>90</td>
<td>M, P</td>
<td>39</td>
<td>2</td>
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<td>2 (Y. N.)</td>
<td>M</td>
<td>35</td>
<td>IgGκ</td>
<td>7.6</td>
<td>33</td>
<td>E, P</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>3 (S. I.)</td>
<td>F</td>
<td>71</td>
<td>IgGκ</td>
<td>9.7</td>
<td>72</td>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4 (T. Y.)</td>
<td>M</td>
<td>73</td>
<td>BJκ</td>
<td>20.7</td>
<td>10</td>
<td>None</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>5 (N. Y.)</td>
<td>M</td>
<td>45</td>
<td>IgGκ</td>
<td>8.2</td>
<td>37</td>
<td>(1) None</td>
<td>8</td>
<td>(1) 8</td>
</tr>
<tr>
<td>6 (S. K.)</td>
<td>F</td>
<td>64</td>
<td>IgAx</td>
<td>6.4</td>
<td>22</td>
<td>M, P</td>
<td>34</td>
<td>(2) 4</td>
</tr>
<tr>
<td>7 (M. H.)</td>
<td>M</td>
<td>71</td>
<td>IgMκ</td>
<td>78.0</td>
<td>90</td>
<td>D, C, 6-MP, P</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

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### Table 2

**Chromosome patterns of patients with PCL and MG**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Source of sample</th>
<th>Date of chromosome study</th>
<th>No. of cells examined (banded)</th>
<th>% of cells with abnormal karyotype</th>
<th>Modal karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M. Y.)</td>
<td>BM</td>
<td>9/21/77</td>
<td>20</td>
<td>100</td>
<td>44, X, Y, +7, +16, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
<tr>
<td>2 (Y. N.)</td>
<td>PB</td>
<td>10/15/77</td>
<td>19</td>
<td>100</td>
<td>44, X, Y, +7, +16, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
<tr>
<td>3 (S. I.)</td>
<td>BM</td>
<td>4/12/79</td>
<td>16</td>
<td>100</td>
<td>44, X, Y, +7, +16, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
<tr>
<td>4 (T. Y.)</td>
<td>PB</td>
<td>12/26/79</td>
<td>38</td>
<td>76</td>
<td>46, XX, Y, +7, +8, +9, +10, +12, +17, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
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<tr>
<td>5 (N. Y.)</td>
<td>BM</td>
<td>1/12/80</td>
<td>14</td>
<td>85</td>
<td>46, XX, Y, +7, +8, +9, +10, +12, +17, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
<tr>
<td>6 (S. K.)</td>
<td>PB</td>
<td>4/24/79</td>
<td>5</td>
<td>0</td>
<td>46, XX, Y, +7, +8, +9, +10, +12, +17, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
<tr>
<td>7 (M. H.)</td>
<td>PB</td>
<td>12/26/79</td>
<td>28</td>
<td>100</td>
<td>46, XX, Y, +7, +8, +9, +10, +12, +17, +18, +19, +21, +22, +2, 4q+, +mar1, +mar2, +mar3, +mar4, +mar5</td>
</tr>
</tbody>
</table>

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a Cases 1 to 6, PCL; Case 7, MG.
b M, melphalan; P, prednisone; E, endoxan; D, daunomycin; C, 1-/α-D-arabinosyl furosycytosine; 6-MP, 6-mercaptopurine.
genetic studies were performed after the leukemic phase developed. There was one normal No. 1, a 1q−, and a 1p− chromosome. The centromere region seemed to be triplicated. Two 14q+ chromosomes of differing size were present; the origin of the extra material was 11q in one of them and remained unclear in another (Fig. 1a).

**Case 2.** Patient Y. N., a 35-year-old man, first noted high fever in December 1978, and PCL was diagnosed in February 1979. He died in November 1979 from systemic complication of infection. Postmortem examination showed plasma cell tumors in the base of the skull, vertebra, ribs, lungs, kidneys, liver, and pleura. The plasma cells were small and ovoid in the peripheral blood and were somewhat immature in the bone marrow and the pleural fluid.

Chromosome studies for bone marrow, peripheral blood, and pleural fluid were performed after 2 cycles of endoxan and prednisone therapy. The long arm of No. 1 was tetrasomic as the result of a large marker which included No. 9 and a duplicated 1q (Fig. 2).

**Case 3.** Patient S. I. first noted general malaise and was admitted to the hospital with a diagnosis of PCL. She died 1 month after admission because of a sudden cerebral hemorrhage. The plasma cells in the bone marrow and peripheral blood were small and immature with scanty cytoplasm, but some of them were somewhat larger than the others. An abnormal clone was found in about 20% of the cells (Fig. 3). There were one normal No. 1 and 3 large markers involving the long arm of No. 1 which were translocated to Nos. 8, 9, and an undetermined chromosome. One chromosome 10 had extra material on the long arm, the origin of which was 1p.

**Case 4.** Patient T. Y. first noted left precordial pain, back pain, nausea, and vomiting, and a diagnosis of PCL was made in December 1979. He had anemia, renal failure, and hepatic dysfunction and died 1.5 months later. Plasma cells in the peripheral blood were immature and atypical for plasma cells. The cells with abnormal chromosomes were near tetraploid, and most of the markers were duplicated (Fig. 1b). Two 14q+ marker chromosomes in addition to 2 normal No. 14 chromosomes were observed which seemed to have a same donor chromosome, but the origin was undetermined. Duplicated large markers involving the 1q and No. 17 were present. There were 6 normal No. 7 chromosomes.

**Case 5.** The clinical course of Patient N. Y. has been reported (12). The plasmacytoid cells in the bone marrow, peripheral blood, and pleural fluid had different morphology (Fig. 4). Cytogenetic studies were performed on 3 occasions. A large marker involving the long arm of No. 1 and No. 16 was consistent in all specimens, while a translocation of No. 15 to 8p and an acrocentric marker appeared only in the pleural fluid. The 14q+ marker was found in the cells from pleural fluid, but it was unclear in the cells from bone marrow and peripheral blood (Fig. 5).

**Case 6.** The clinical course of Patient S. K. has been reported (13). Chromosome studies were attempted on several occasions, but only 2 samples had mitotic cells. Most markers seemed to be duplicated (Fig. 1c). Duplicated sets of a marker involving the 1q were present, but the other chromosome could not be determined. There were two normal No. 7 chromosomes, and two 7p+ chromosomes which contained a duplicated segment of 7q21 to 7qter.

**Case 7.** Patient M. H. was well until 1 month before admission when he noticed left chest pain. He was hospitalized in December 1979 because of mental confusion. He had hypercalcemia, anemia, leukocytosis, and serum monoclonal IgM, and the diagnosis of MG was made. He died in October 1980 from a generalized infection. Chromosomes were studied 1 month after admission. No cells had a normal X, but it was possible that the X chromosome was involved in the marker (Fig. 1d). The long arm of No. 1; segment q12-qter was trisomic and q12-q21 was tetrasomic in about one-half of the cells.

**DISCUSSION**

Chromosome studies in our series revealed a high incidence of clonal chromosomal abnormalities in PCL. Four series of prebanding studies (1, 3, 10, 23) and 2 series of banding studies containing 10 or more cases of plasma cell dyscrasias have been published (11, 16, 29). The incidence of chromosomal abnormalities varied from 28 to 87%. In stable MM, myeloma cells in division occur much less frequently than do their normal counterparts, because of their long generation time (11). In the accelerated phase of MM, a higher percentage of abnormal karyotypes has been reported (11), but it is still difficult to estimate the overall frequency. The high incidence in our series could be due to the accelerated clinical stage in the cases; we could, therefore, study the spontaneously dividing myeloma cells.

The frequent involvement of No. 1 and the presence of the large marker chromosomes involving the long arm of No. 1 seemed to be characteristic of MM, especially in the leukemic phase of MM. All 7 cases including the case of MG had the abnormalities of No. 1, and 6 of them had the large marker involving the 1q in our series. The large markers involved the long arm of No. 1 and various other chromosomes. The translocations occurred with Nos. 8, 9, 16, 17, and 18 in our series; Nos. 3 and 10 in the reported cases of PCL; and Nos. 12, 15, and 16 in the MM series. Two large markers involving the 1q were found in the patient with MG in our series. The translocations occurred with Nos. 16 and 18. These markers seemed to be similar to the markers seen in other patients with PCL. Thus, the large markers involving the 1q could be common in MM, PCL, and MG. Although other large markers were present which did not involve the 1q, but involved No. 2 or No. 3 (Fig. 1), it was suggested from our results that most of the large markers may involve the long arm of No. 1 in MM and PCL.

The presence of the large marker chromosomes resulted in trisomy, tetrasomy, or hexasomy of the long arm of No. 1 in all 6 cases with the large marker which involved the long arm of No. 1. Rowley proposed that trisomy for bands 1q25-1q32 provides the affected cells with a proliferative advantage in various hematological disorders (17). In the MM series, the significantly shorter survival time was reported for 5 patients with trisomy for the 1q12-1q3 section (16). In our series, 5 patients with an extra 1q had a fulminant course and died within 1 year, and only one lived for over 2 years. She had generalized plasmacytoma, however, and died 2 months after the chromosome study.

Two of 7 cases of PCL in the literature have trisomy 1q (11, 16, 26) (Table 3). Their survival times are 41 and 13 months, respectively, after diagnosis. The longer survival case had expanded infiltration of myeloma cells at the autopsy. Another had trisomy 1q in the side line and died 1 month after the
chromosome examination. Thus, the rearrangement of No. 1, especially the gain of the long arm of No. 1, might be associated with leukemic evolution of myeloma cells.

The 14q+ marker has been recognized as the most consistent structural aberration in PCL (11, 16, 29). Six of 7 cases of PCL in the literature (8, 11, 16, 26, 29) have been reported to have a 14q+ marker, and the remaining one is suspected to be a secondary leukemia, because she is missing chromosomes 5 and 7 (16, 26). Four of 18 patients with MM have a 14q+ marker, and it has been suggested that the 14q+ marker is necessary for the evolution of B-cell leukemias (16). In our series, however, only 3 patients had the 14q+ marker, and the remaining 4 did not. The incidence of the 14q+ may be higher in PCL than in MM, but the 14q+ chromosome does not appear to be necessary for leukemic evolution of myeloma cells. The identification of the donor chromosomes to 14q has been difficult in MM or PCL, because the banding pattern is often poor, and the rearrangements are complex (11, 16). The origin of the 14q+ has been determined as t(11;14) in 3 and possibly t(11;14) in one patient with PCL and has not been determined in the remaining patients with MM or PCL (11, 16, 29). One of five 14q+ chromosomes from three patients in our series was a t(11;14), but the others remained undetermined. The size and banding pattern of each 14q+ chromosome differed from the 14q+ originating from 11q, which suggests different donors. Our results suggest the 14q+ chromosomes in MM and PCL are not uniform as t(8;14) in Burkitt lymphoma, but some different donors may participate in the formation of the 14q+ chromosomes.

It appears that almost every chromosome was involved and that the chromosome pattern was variable both in our series and in the reported cases of plasma cell dyscrasia. The pattern of the abnormalities, however, seemed to have some characteristic differences from that in myelogenous leukemia, malignant lymphomas or lymphocytic leukemias. No cases in our series showed a loss of No. 5 or No. 7 which have been often reported in acute myelogenous leukemia and secondary acute nonlymphocytic leukemia (19, 20, 27). No cases had an additional No. 12 which has been suggested to be a consistent aberration in chronic B-cell lymphocytic leukemia (7). Instead of these, all 7 patients had abnormalities of No. 1, 3 had the 14q+ marker, 5 had rearrangements or deletion of 8p, 3 had a rearrangement of 9p, 2 had extra No. 7 chromosomes or 7q+, and one had a 6q− chromosome. Loss of sex chromosome was found in 5 patients, and loss of chromosomes 13 or 22 was found in each of 2 patients. The loss of a sex chromosome has sometimes been found in other hematological cancers (20). The 14q+ chromosome, gain of No. 7 or 9, and the 6q− chromosome may be lymphoid markers which may be common in T-, B-, and non-T, non-B cancers (5, 6, 14, 18, 20, 25). The high incidence of the abnormalities of No. 1, especially the large markers including 1q, deletion or rearrangements of 8p, rearrangement of 9p, and loss of No. 13, could be characteristics for PCL, MM, or B-cell cancers.

Two series with banding containing 4 cases with PCL and 14 cases with MM with abnormal karyotypes have been reported (11, 16). Although 5 other cases with PCL have been reported, 2 are cell line studies (2, 4). One was reported to have a 14q+ chromosome, but the details are lacking (29) and another case (26) could be secondary leukemia. The gain of No. 9 in MM is significantly higher than in the malignant lymphoma series (p < 0.001). Nine of 14 patients with MM have a gain of No. 9, compared with 3 of 114 cases with lymphoma reviewed by Sandberg (20). No patient in our series or in the reported cases of PCL had a gain of No. 9, and it could be one of the differences between PCL and MM, although the number is too small to be certain. Instead of the gain of No. 9, a rearrangement of 9p was observed in 3 and a 9q+ was observed in one patient in our series. Translocations occurred with the long arm of No. 1 in 3 of them. The rearrangement of 9p could be one of the characteristics of PCL.

In the MM series, the incidence of loss of No. 8 seems to be higher than in the lymphoma series. In the series of Liang et al. (11), a missing No. 8 chromosome was reported in 4 of 6 patients with MM; in one of them, it was observed only in the second sample which was obtained 9 months after the first sample. In our series, 5 patients had rearrangements or deletions of 8p. One patient had a translocation of No. 15 to 8p; this was noted in the third sample which was obtained 4 months after the second sample. Thus, the loss of No. 8 or rearrangement of No. 8 appears to be a common aberration associated with the karyotypic evolution of myeloma cells.
We have shown that the markers involving 1q and another chromosome and rearrangements or deletions of 8p or 9p are common in PCL. These are sometimes observed in MM but are infrequent in other B-cell disorders. Other investigations have identified different patterns in Burkitt’s lymphoma where translocations commonly involve 8q and in poorly differentiated lymphocytic lymphoma where a t(14q+;18q-) is seen in the majority of cases. Thus, careful cytogenetic analysis can provide information that contributes to the further characterization of malignant disorders of lymphoid cells.

ACKNOWLEDGMENTS

We are very grateful to Dr. Janet D. Rowley for critical review.

REFERENCES

Fig. 1. Partial karyotypes of G-banded (a) and Q-banded (b to d) cells illustrating some of the abnormalities in cells from Cases 1 (a), 4 (b), 6 (c), and 7 (d). A complete description of the karyotype is included in Table 2. i, der(17)t(1;17)(q12;p13); ii, markers involving 1q and unknown chromosomes; iii, der(16)t(1;16)(q12;p13); iv, der(18)t(1;18)(q12;p13).

Fig. 2. Q-banded karyotype of a cell from Case 2. The abnormal chromosomes t(6;8)(q13;p11), der(9)t(1;9)(q12;p13→q44→p12→q34→p13) and the missing Y chromosome and No. 13 are indicated with arrows.
Chromosomes in PCL

Fig. 3. Q-banded karyotype of a cell from Case 3. The abnormal chromosomes including a marker involving 1q and an unknown chromosome, der(8)t(1;8)(qter→cen→8qter), der(9)t(1;9)(q21;p24), der(10)t(1;10)(p31;q26), a missing X chromosome and missing Nos. 13 and 22 are indicated with arrows.

Fig. 4. Examples of abnormal cells from Case 5 at various stages of his disease. a, myeloma cells in the bone marrow aspirate at the time of diagnosis. May-Giemsa, × 1000. b, atypical plasmacytoid cells with convoluted nuclei in peripheral blood during the leukemic phase. × 400. c, myeloma cells in the pleural effusion before death. × 100.
Fig. 5. Q-banded karyotype of a cell from the pleural effusion in Case 5. The abnormal chromosomes 4q+, 6q−, der(8)t(8;15)(p23;q12), 14q+, der(16)t(1;16)(q21;p13), a missing No. 15, and missing No. 18 are indicated with arrows. The missing No. 13 is due to random loss of this chromosome.
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