The Clinical Significance of Cytogenetic Studies in 100 Patients With Multiple Myeloma, Plasma Cell Leukemia, or Amyloidosis

By Gordon W. Dewald, Robert A. Kyle, Gary A. Hicks, and Philip R. Greipp

MULITPLE MYELOMA (MM) and primary systemic amyloidosis (AL) are B cell disorders that, in their earliest stages, may be recognized only as a monoclonal gammapathy of undetermined significance. They may slowly progress or become aggressive and evolve into overt plasma cell leukemia (PCL). In the early stages, observation is sufficient, but in the symptomatic stages, chemotherapy is needed. The situation is complicated by the fact that treatment-related leukemia may develop in some of the treated patients.1

The purpose of this prospective study of 100 patients was to investigate the chromosome abnormalities in MM and related disorders and to determine whether cytogenetic studies could (1) help in diagnosis, (2) provide useful survival information, (3) aid in the early detection of progressive disease or the development of leukemia, and (4) contribute to the management of patients with plasma cell disorders. We are aware of only five cytogenetic studies using banding methods on ten or more patients with such a disorder.2-4

Materials and Methods

Chromosome analyses were done on bone marrow aspirates whenever possible. In some cases, bone marrow biopsy specimens

With all abnormal metaphases and eight months for patients with normal and abnormal metaphases and has not yet been reached for patients with only normal metaphases. The most common anomalous chromosomes in patients with a plasma cell proliferative disorder were 1, 11, and 14. 11 patients had an abnormality involving chromosome 14q32 and nine patients had an abnormal chromsome 11. The single most common abnormality, a t(11;14)(q13;q32), occurred in three patients. Among the patients who developed preleukemia or acute nonlymphocytic leukemia, the most common anomaly involved chromosome 7. The results suggest that cytogenetic studies are valuable for identifying patients who have a poor prognosis and can help distinguish patients with a cytopenia because of preleukemia from those with an aggressive plasma cell proliferative process.

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phases were found. Among the 100 remaining patients, 82 had MM, 11 had AL, 2 had MM and AL, and 5 had PCL. The median age, sex, and the number of patients in each of the six clinical categories are shown in Table 1. The median age at the time of chromosome analysis for all patients was 65 years; 58% were men and 42% were women. Thus, with respect to age and sex, our patients were similar to other series of patients with MM and related disorders.14,15

Techniques. Of the 100 patients, 19 underwent two chromosome analyses, and 81 were studied once. Among the 19 patients who were studied twice, the results were concordant in 12; the second study revealed a chromosomally abnormal clone whereas the first study did not in two patients; the results of the first study were abnormal when those of the second study were not in one patient; and only one of the two studies involved five or more suitable metaphases in four patients. Thus, multiple studies increase the chances of finding a chromosomally abnormal clone.

Chromosome analyses were done on bone marrow aspirate from 99 patients, and five or more suitable metaphases were found in 98. The studies were successful in all 26 patients investigated with only the direct technique and in 22 of the 23 patients investigated with only a short-term culture method. Chromosomally abnormal clones were observed in 12% (three of 26) of the direct studies and in 18% (four of 22) of the short-term cultures. Both direct and short-term culture methods were used to investigate 50 patients. At least one of the two methods was successful in each instance, and a chromosomally abnormal clone was found in 36% (18 of 50) of the patients. In eight cases with abnormal clones, the results were similar by both methods. In five instances the direct technique revealed an abnormal clone when the short-term culture did not, and in five other cases the short-term culture revealed an abnormal clone when the direct method did not. Thus, chromosome analysis was equally successful with the direct technique and the short-term culture, but the combined use of the two methods increased the chances of finding a chromosome abnormality.

A bone marrow biopsy specimen was studied in nine patients; five or more metaphases were observed in seven and a chromosomally abnormal clone was found in four. Thus, chromosome analysis of bone marrow biopsy specimens seems to be at least as informative as that of bone marrow aspirates. Peripheral blood was studied in five patients; the studies were successful in three but only one had a chromosomally abnormal clone. In two patients with PCL, studies of the blood specimen were successful when a bone marrow aspirate was either unavailable or inadequate. Pleural effusions were investigated in two patients; the study was successful in one and a chromosomally abnormal clone was found.

Correlation of chromosome pattern (AA, AN, and NN) with diagnosis and clinical state. A chromosomally abnormal clone was found in 29 of the 100 patients: in 22 (27%) of the 82 patients with MM, five (46%) of the 11 with AL, and two (40%) of the five with PCL. No chromosome abnormality was found in the two patients with MM and AL. The numbers of patients whose chromosome patterns were classified as AA, AN, or NN in each clinical category are shown in Table 2.

Chromosomally abnormal clones were found more frequently in the advanced stages of disease than in the early stages. Of the 16 patients with aggressive MM resistant to therapy, ten (63%) had a chromosomally abnormal clone, as did two (40%) of the five patients with PCL. In comparison,
none of the five patients with smoldering myeloma and only six (18%) of the 33 patients with untreated MM or AL had a chromosomally abnormal clone. An abnormal clone was found in two (12%) of the 17 patients who had responded to therapy and in nine (38%) of the 24 treated patients who had cytopenia.

**Correlation of chromosome pattern (AA, AN, and NN) with survival.** The duration of follow-up ranged from 14 to 874 days, but in 79% of the cases it was longer than 90 days. Of the 100 patients, 49 have died, and 43 survived for one year or more. The survival distributions according to cytogenetic classification (AA, AN, and NN) relative to the time of chromosome analysis were significantly different (P = .001) (log rank test). The median survival of the 13 patients with AA patterns was three months; all 13 have died and only two survived one year or more. The median survival for the 16 patients with AN patterns was eight months; 12 have died and five survived one year or more. Most of the patients with AA and AN patterns had acute leukemia or aggressive myeloma. The median survival of the 71 patients with NN patterns has not been reached; 24 have died and 36 (51%) have survived one year or more. Most of these patients had low-grade myeloma or smoldering myeloma. A chromosomally abnormal clone seems to be associated with a poor prognosis.

Survival curves for 32 patients with untreated MM (of the 33 patients with untreated disease, the patient with AL was excluded) according to the cytogenetic classifications (AA, AN, or NN) are shown in Fig 1. The differences among these curves are statistically significant (P = .0089). The median survival for the six patients with AA and AN metaphases was six months and four have died. The median survival of the 26 patients with NN metaphases has not been reached because only six have died; however, it will be more than 12 months. Three of the six patients with an abnormal clone developed an aggressive myeloma within three months and died at 2, 4, and 12 months after chromosome analysis. A patient with preleukemia died within two months of infectious complications from neutropenia. One of the other chromosomally abnormal patients is alive at 13 months after study but has symptomatic refractory myeloma. The abnormal clone of the sixth patient was lacking only a Y chromosome; this patient has stable myeloma and is alive at four months after analysis.

The durations of survival of patients classified by subset of disease were statistically different (P = .004). Four of the five patients with PCL have died (median survival, three months), and 14 of the 16 patients with aggressive disease have died (median survival, six months). The patients who responded to treatment had the best survival—only four of 17 patients have died. Within each group, the survival curves for patients with AA and AN metaphases were associated with shorter survival than for those with NN patterns; however, except for the untreated group, the differences were not statistically significant. The sample size precluded an appropriate statistical evaluation.

A stepwise proportional hazards test was used to determine which of the following variables were most closely associated with survival: presence or absence of a chromosomally abnormal clone, subset of disease, age, and sex. Only the presence or absence of a chromosomally abnormal clone and the subset of disease proved to have any statistically significant effect on survival. Of these two factors, a chromosomally abnormal clone indicated a worse prognosis than did the clinical manifestations of disease.

**Karyotypes of abnormal clones.** Seven patients had no apparent structural anomaly of any chromosome but did have an aneuploid clone (Table 3). Monosomy 7 occurred in three patients: one had AL with cytopenia and developed acute leukemia, and two had MM with cytopenia. In one of the two patients with MM, a myelodysplastic syndrome developed, but the other patient has no evidence of leukemia. One patient had trisomy 15 and another had trisomy 19; both had MM with cytopenia and developed a myelodysplastic syndrome. In four of these five patients, the aneuploid clones were associated with a leukemic process. Two patients had an abnormal clone that lacked a Y chromosome; one had untreated MM and one had treated AL. Thus, the clones lacking only a Y chromosome may not be associated with plasma cell proliferative processes.

In 22 patients, the chromosomally abnormal clone contained one or more structurally abnormal chromosomes. The three most common anomalous chromosomes were 1, 11, and 14. Representative abnormalities of these chromosomes are shown in Fig 2 through 4. The modal karyotype for each of the 22 abnormal clones is listed in Table 3.

A 1q+ chromosome occurred in 11 patients: three had untreated MM, one had treated AL, one had treated MM and cytopenia, four had aggressive MM resistant to therapy, and two had PCL. Because chromosome 14 anomalies were found in untreated patients and in many patients without cytopenia, they are likely to be associated with the plasma cell proliferative process. In three patients, the 1q+ anomaly was derived from an 11;14 translocation [t(11;14)(q13;q32)]; one had PCL, one had aggressive MM resistant to therapy, and one had untreated MM. In another patient, the 1q+ was from a 13;14 translocation [t(13;14)(q22;q32)]; this patient had aggressive MM resistant to therapy. We were unable to establish the origin of the
extra chromatin on the 14q+ chromosome in the other seven patients: one had PCL, two had aggressive MM resistant to therapy, one had treated MM with cytopenia, one had treated AL, and two had untreated MM.

Thirteen patients had one or more abnormalities of chromosome 1: four had untreated MM, one had AL and cytopenia, six had aggressive MM resistant to therapy, and two had PCL. Thus, anomalies of chromosome 1 also seem to be associated with plasma cell proliferative processes. Six patients had a deletion of part of a chromosome 1 short arm: three had aggressive MM resistant to therapy, one had treated AL with cytopenia, and two had untreated MM. In five of the six, the deletion appeared to be interstitial; in most instances the breakpoints were at 1p11 and 1p22. The sixth deletion appeared to be terminal [del(1)(p32)]. Six patients had a translocation involving chromosome 1; in most instances, the chromosome 1 breakpoint was in the pericentromeric region in either band 1p11 or band 1q11. One of these patients had PCL, four had aggressive MM resistant to therapy, and one had untreated MM. In one of these patients the abnormal chromosome 1 was from a 1;18 translocation [t(1;18)(p36;p11)], and in another it was a 1;21 translocation [t(1;21)(q11;q22)]. In addition to these deletions and translocations, one patient with untreated MM had an isochromosome of the long arm of chromosome 1 [i(1q)] and one patient with PCL had a direct duplication of the proximal half of the long arm of a chromosome 1 [dirdup(1)(q21→q32)].

Nine patients had an abnormality of chromosome 11: two had untreated MM, one had AL with cytopenia, four had aggressive MM resistant to therapy, and two had PCL. Thus, an anomalous chromosome 11 also seems to be associated with plasma cell proliferation. Three of these patients had a 14q+ anomaly as a consequence of an 11;14 translocation [t(11;14)(q13;q32)], as described previously. In addition, one patient with untreated MM had an 11;13 translocation with a breakpoint on the long arm of chromosome 11 [t(11;13)(q23;q14)]. Three other translocations in patients with aggressive MM resistant to therapy involved the short arm of a chromosome 11 (11p13 or 11p15), but we were unable to establish the origin of the additional chromatin. In addition to these translocations, two patients had a deletion of the short arm of a chromosome 11 [del(11)(p11)]: one patient had treated AL with cytopenia and the other had PCL.

Three patients had an abnormality of chromosome 6: two had untreated MM and one had aggressive MM resistant to therapy. Two of these patients had a deletion of part of the long arm [del(6)(q21) and del(6)(q23)]: one had aggressive MM resistant to therapy and one had untreated MM. One patient with untreated MM had a Y;6 translocation [t(Y;6)(q11;q23)].

Two patients had an anomalous chromosome 20. A patient with aggressive MM resistant to therapy had a deletion of a portion of the long arm [del(20)(q13)], and a patient with PCL had excess chromatin translocated onto a chromosome 20 long arm, but we were unable to establish its origin [t(20;?)q13;?].

Four patients had an anomalous chromosome 7: one was a long arm deletion [del(7)(q11)] and the other three were derived from different translocations [t(7;21)(q11;q11), t(7;7)(p22;?), and t(7;9)(q22;q22)]. Two of these patients (patients No. 9 and 16) had cytopenia and developed acute nonlymphocytic leukemia (ANLL). The other two patients (patients No. 18 and 21) had aggressive MM resistant to therapy with no evidence of preleukemia.

Two patients had deletion of part of a chromosome 5 long arm [del(5)(ql3;q31)]. One of these patients (patient No. 9) had MM with cytopenia and developed ANLL. The other patient (patient No. 19) had aggressive MM resistant to therapy but no evidence of leukemia. All patients with an anomalous chromosome 5 or 7 lacking a chromosome 5 or 7 had undergone chemotherapy and four had ANLL.

Abnormalities in plasma cell proliferative disorders. The chromosome abnormalities found in patients with only a plasma cell proliferative disorder were different from those in patients with MM or AL and cytopenia. The frequency of anomalous chromosomes for the 20 patients with only a plasma cell proliferative process and the nine patients with either MM or AL and cytopenia is shown in Fig 5. Abnormalities of chromosomes 1, 11, and 14 were the most frequent anomalies among the patients with only a plasma cell disorder. By comparison, abnormalities of chromosome 7 were most common among the patients with MM or AL and cytopenia.

Of the six untreated patients with a chromosome abnormality, four had structural abnormalities of chromosomes 1, 11, or 14 or some combination of these three chromosomes. A fifth patient (patient No. 6) had a de novo myelodysplastic process in addition to MM. Thus, his abnormal clone (45,X,-Y,-1,-3,-4,-5,-6,-10,-16,-19,-20,+9) could be related to either MM or a myelodysplastic syndrome. The sixth patient (patient No. 4) lacked a Y chromosome.

The two chromosomally abnormal patients with PCL had chromosome abnormalities similar to those of the untreated patients: one had a duplication of part of chromosome 1 and a 14q+ chromosome, and the other had a 1p+ and an 11;14 translocation. In addition, eight of the ten patients with aggressive MM resistant to therapy also had chromosome abnormalities similar to those found in patients with untreated MM; the abnormalities involved chromosome 1 in six patients, chromosome 11 in four, and chromosome 14 in four.

In contrast, six of the nine patients with cytopenia were monosomy 7 or had a structurally abnormal chromosome 7. Only two of these patients had an abnormality of chromosomes 1, 11, or 14. Of the nine patients, five eventually developed overt ANLL, three had a myelodysplastic syndrome, and one had pronounced cytopenia but died before leukemia developed.

Chemotherapy and abnormalities of chromosomes 5 and 7. All nine of the chromosomally abnormal patients with cytopenia had chemotherapy prior to chromosome analysis; five eventually developed ANLL and three had a myelodysplastic syndrome. Six of these patients had a structural
### Table 3. Chromosome Abnormalities in 29 Patients with a Monoclonal Gamopathy

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>Patient No.</th>
<th>Dx*</th>
<th>Other Dx†</th>
<th>Immunoglobulin</th>
<th>Survival (mol%)</th>
<th>Tissue§</th>
<th>Method</th>
<th>Cells</th>
<th>Classification</th>
<th>Modal Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated MM or AL</td>
<td>1</td>
<td>MM</td>
<td>—</td>
<td>K</td>
<td>12</td>
<td>Bx</td>
<td>24 h</td>
<td>33</td>
<td>AA</td>
<td>33 = 46, X,−X,−13,+i(1q), t(8:10)(q11:p11), t(11;14)(q13;q32), +mar</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>MM</td>
<td>—</td>
<td>K</td>
<td>2</td>
<td>BM</td>
<td>24 h</td>
<td>13</td>
<td>AA</td>
<td>13 = 51, X,−X,−1,+4,+5,+7,−13,−15,−15,−21,+del(21)(q11:q21)</td>
</tr>
</tbody>
</table>
|                   |             |     |           |                |                |          |        |       | (q11:q22), +del(6)(q23), +del(7)(q23), +del(11), +del(11), +del(13)(q23:q32), +2mar |}
|                   | 3           | MM  | —         | K              | 12             | BM       | Dir    | 20    | AN             | 11 = 46,XY/9−49,X,+4,+9,+11,(t(7;16)(q11:q23), +del(11)(p11:p22)) |
|                   | 4           | MM  | —         | Neg AL         | 4              | BM       | 24 h   | 30    | AN             | 3 = 46, X,Y/27−46, XY |
|                   | 5           | MM  | —         | K              | 2              | BM       | Dir    | 21    | AN             | 19 = 46,XY/2−49,X,−Y,+3,+4,(del(1)(p11:p22),t(14:q23), +2mar | |
|                   | 6           | MM/MS| —         | L + GL         | 2              | BM       | 24 h   | 20    | AN             | 20 = 45, X−Y,−1,−3,−4,−5,−6,−10,−16,−19,−20, +9mar | |
| Treated MM or AL  | 7           | AL  | —         | GK + K         | 11             | BM       | Dir    | 40    | AN             | 18 = 45, X−Y/22−46, XY |
|                   | 8           | AL  | —         | L              | Neg  | BM       | Dir    | 24 h  | 30   | AN             | 32 = 36,XY/2−46,XY,t(14:q32), +2mar | |
| Treated MM or AL  | 9           | MM  | ANLL M6   | Neg            | 2              | BM       | 24 h   | 30    | AN             | 30−44, XY,−7,−14,del(5)(q13q31),t(7:q22),t(14:q23),t(19:q31), +2mar | |
|                   |             |     |           |                |                |          |        |       | (q31:?)        | (p13:7:1) = 8−187 by 188 chromosomes with many mers | |
|                   | 10          | MM  | ANLL M2   | L              | GL             | PB       | 24 h   | 20    | AN             | 12 = 45, X−Y, t(17:1)(p13:5:1)/8−187 by 188 chromosomes with many mers | |
|                   | 11          | MM  | MS        | Neg            | 12             | BM       | Dir    | 24 h  | 20   | AN             | 16 = 46,XY/4−47,XY, +15 | |
|                   | 12          | MM  | MS        | K              | AK             | 4        | BM     | Dir    | 24 h | 30   | AN             | 28 = 46,XY/2−47,XY, +99 | |
|                   | 13          | MM  | MS        | K              | Neg            | 16       | BM, Bx | 24 h  | 30   | AN             | 8 = 45,XX−7−22−46,XX | |
|                   | 14          | MM  | ?         | L              | Neg            | 19       | BM     | Dir    | 24 h | 56   | AN             | 35 = 45,XX−7−21−46,XX | |
|                   | 15          | AL  | ANLL M2   | K              | Neg            | 5        | BM     | Dir    | 24 h | 33   | AN             | 33 = 45,XX,−4,−5,−7,−12,−14,−21, t(4:q35), +t(12:q3) | |
|                   |             |     |           |                |                |          |        |       | (p12:q1) +3mar | | |
|                   | 16          | AL  | ANLL M2   | L + GL         | GL             | 1        | BM     | Dir    | 24 h | 40   | AN             | 40 = 46,XX, +del(1)(p34p36), t(7:9)(q32:q22), +del(11)(p11) | |
|                   | 17          | AL  | ANLL M2   | Neg            | Neg            | 5        | BM     | Dir    | 24 h | 61   | AN             | 21 = 45,XX,−7−40−46,XX | |
| Aggressive MM     | 18          | MM  | ?         | L              | L              | 12       | BM     | Dir    | 24 h | 20   | AN             | 1 = 46,XY/19−46,XY, +del(7)(q11), +del(20)(q13) | |
| resistant to      | 19          | MM  | ?         | K              | Gk             | 8        | BM     | Dir    | 24 h | 40   | AN             | 24 = 46, XY/13−46,XY, +del(5)(q13q31), +1−hyperdiploid with 5q− | |
| therapy           | 20          | MM  | —         | K              | Gk             | 1        | BM, PE | Dir    | 24 h | 40   | AN             | 40−53, X−X,+6,+11,+14,+15,+18,+19,+21,+21, +der(1), t(1:1)(p11:q1), +der(14), t(11:14)(q13:q32), +der(11), +der(11) | |

§ Tissue: Bx = bone marrow, PB = peripheral blood, BM = bone marrow.
† Other Dx: ANLL = acute non-lymphocytic leukemia, MDS = myelodysplastic syndrome, MS = multiple myeloma, MM = multiple myeloma, AL = amyloidosis.
<table>
<thead>
<tr>
<th>Case</th>
<th>MM</th>
<th>K</th>
<th>AK</th>
<th>Tissues</th>
<th>Dir</th>
<th>Time</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>MM</td>
<td>K</td>
<td>AK</td>
<td>BM, PB</td>
<td>24h</td>
<td>34</td>
<td>AA: 34-47,XY; -2,-4,-6,-7,-8,-10,-11,-12,-16,-17,+19, +20, +t(1;18)(p36;p11), +der(7;7)(q11;q11), +der(11),t(11;11)(p13;p13), +t(11;12)(p13;p13), +5mars</td>
</tr>
<tr>
<td>22</td>
<td>MM</td>
<td>K</td>
<td>K</td>
<td>BM, Bx</td>
<td>24h</td>
<td>11</td>
<td>AA: 11-46,XY,+3,-13,-14,+21,del(1)(p32p36)</td>
</tr>
<tr>
<td>23</td>
<td>MM</td>
<td>L</td>
<td>GL</td>
<td>BM</td>
<td>24h</td>
<td>39</td>
<td>AN: 12-46,XX/27-47,XX,+18,t(13;14)(q22;q32)</td>
</tr>
<tr>
<td>24</td>
<td>MM</td>
<td>L</td>
<td>GL</td>
<td>BM</td>
<td>24h</td>
<td>24</td>
<td>AN: 17-46,XY/783,XX,-Y,+2,+3,+4,+4,+5,+6,+6,+8,+8,+9,+10,+11,+12,+14,+15,+16,+16,+17,+18,+18,+20,+20,+21,+21,+22,+del(1)(p32), +t(14;7)(q32;7), +del(14), t(14;7)(q32;7), +12mars</td>
</tr>
<tr>
<td>25</td>
<td>MM</td>
<td>L</td>
<td>GL</td>
<td>BM</td>
<td>25h</td>
<td>25</td>
<td>AN: 6-46,XY/19-83,XXYY,+2,+3,+3,+4,+5,+5,+7,+8,+9,+10,+15,+16,+17,+20,+21,+21,+22,+22,+t(11;7)(p15;7), +der(11),t(11;7)(p15;7), +t(11;7)(p15;7), +del(6)(q21), +del(6)(q21), +t(14;7)(q32;7), +12mars</td>
</tr>
<tr>
<td>PCL</td>
<td>MM</td>
<td>K</td>
<td>GK</td>
<td>BM</td>
<td>24h</td>
<td>33</td>
<td>AN: 27-46,XX/147,XX,1p/+5=57 to 161 chromosomes with many mars</td>
</tr>
<tr>
<td>27</td>
<td>MM</td>
<td>L</td>
<td>DL</td>
<td>BM</td>
<td>27h</td>
<td>27</td>
<td>AN: 22-46,XY/52,XY,-1,-3,t(11;7)(p15;7), +8mars</td>
</tr>
<tr>
<td>28</td>
<td>PCL</td>
<td>L</td>
<td>AL</td>
<td>BM</td>
<td>24h</td>
<td>43</td>
<td>AA: 43-44,X,-X,-8,-9,-11,-16,-18,dir dup(1)(q21→q32), del(11)(p11),del(13)(q14),t(14;7)(q32;7),t(19;7)(p13;7),t(20;7)(q13;7), +4mars</td>
</tr>
<tr>
<td>29</td>
<td>PCL</td>
<td>G</td>
<td>GK</td>
<td>BM</td>
<td>24h</td>
<td>5</td>
<td>AA: 5-49,XY,-6,-11,-17,der(1),t(1;1)(p11;7),t(11;14)(q13;q32), +5mars</td>
</tr>
</tbody>
</table>

*Diagnosis at time of chromosome analysis: AL, amyloidosis; MM, multiple myeloma; MS, myelodysplastic syndrome; PCL, plasma cell leukemia.
†Diagnosis of another disorder subsequent to time of chromosome analysis: ANLL M2 (M6), acute nonlymphocytic leukemia; MS, myelodysplastic syndrome; ?, possible myelodysplastic disorder; ---, none apparent.
‡Months of survival from time of chromosome analysis: +, patient is alive.
§Only tissues that produced chromosomally abnormal clones are listed. BM, bone marrow aspirate; Bx, bone marrow biopsy specimen; PB, peripheral blood; PE, pleural effusion.
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abnormality of chromosome 5 or 7 or monosomy 5 or 7. Thus, chemotherapy for plasma cell proliferative disorders apparently can lead to leukemia that is often associated with abnormalities of chromosomes 5 or 7 or both. Two other patients (patients No. 18 and 19) also had undergone chemotherapy for MM and had a chromosomally abnormal clone involving a chromosome 5 or 7. Both of these patients had aggressive MM and were resistant to therapy at the time of chromosome analysis. These two patients have died, but because their chromosome abnormalities resembled leukemia rather than MM, we suspect that they might have had a myelodysplastic process in addition to MM.

**Chromosome abnormalities and progression of MM.** Of the 33 patients with untreated MM or AL, 31 had MM, one had AL, and one had MM and AL. The conditions were diagnosed at the time of chromosome analysis in 28 of the patients, and the five others had had their disease from five to 34 months.

Of the 33 patients, six had a chromosomally abnormal clone. One of these patients (patient No. 6) also had de novo preleukemia and died two months after chromosome analysis. The five other patients all had MM (three were newly diagnosed and two had had MM for 12 and 16 months) but all soon developed aggressive MM: three of the patients have died, surviving from two to 12 months after cytogenetic studies. One patient (patient No. 3) has survived 13 months but has resistant MM; his chromosome pattern was AN and the karyotype of his abnormal clone was

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**Fig 2.** Representative abnormalities of chromosome 14 from five patients with multiple myeloma (MM). See Table 3 for more cytogenetic and clinical information about these patients.

**Fig 3.** Representative abnormalities of chromosome 1 from eight patients with plasma cell proliferation. Patients 28 and 29 had plasma cell leukemia (PCL); patient 16 had amyloidosis (Al), and the other five patients had multiple myeloma (MM). See Table 3 for more cytogenetic and clinical information about these patients.
49,X,+4,+9,+11,t(Y;6)(q11;q23),del(1)(p11p22). Another patient (patient No. 4) has survived four months; his chromosome pattern was AN and his abnormal clone lacked only a Y chromosome. The observation of a chromosomally abnormal clone in an untreated patient with MM indicates a poor prognosis.

The 27 remaining patients with untreated MM or AL had normal karyotypes at the time of chromosome analysis: their median survival has not been reached but seven have died and 12 have survived one year or more. Thus, the observation of only normal metaphases in an untreated patient with MM portends a better prognosis than that of a chromosomally abnormal clone.

Cytogenetics and monoclonal proteins. We correlated the cytogenetic results with the type of monoclonal protein in the serum and urine at the time of chromosome analysis for the 29 patients with a chromosomally abnormal clone (Table 3): three patients with cytopenia and one with untreated MM had no monoclonal protein; in the 25 other patients, the light chain component was K in 14 and L in 11. A heavy chain component was present in 19 patients: in 14 patients it was IgG, in four it was IgA, and in one it was IgD. No significant associations between the type of chromosome anomaly and the monoclonal proteins were apparent.

DISCUSSION

Frequency of chromosome abnormalities in plasma cell disorders. Of the 67 reported patients with a plasma cell proliferative process who had a chromosomally abnormal clone identified with modern cytogenetic banding techniques, 49 had MM, 14 had PCL, and four had macroglobulinemia. Most of these studies were reviewed by Philip, and the karyotypes for the majority of the patients were cataloged by Mitelman. However, most of
the reported patients with plasma cell proliferative disorders have been chromosomally normal. Nevertheless, we agree with the investigators who suggest that all patients with a malignant plasma cell proliferative process may have a chromosomally abnormal clone, although such clones are not always recognized during routine chromosome studies. The major reason for not finding an abnormal clone in such patients is that malignant plasma cells undergo cell division infrequently and so are not easily discovered.

This report constitutes the largest series of patients with plasma cell disorders studied with chromosome-banding techniques; we found a chromosomally abnormal clone in 29 of our 100 patients. We are aware of only five other reports involving ten or more patients. Liang et al investigated 18 persons with MM, six (33%) of whom had a chromosomally abnormal clone. Of the 25 persons with MM studied by Philip et al., 16 (64%) had a chromosomally abnormal clone. Elemer et al found that of ten patients with MM, five (50%) had a chromosomally abnormal clone. Ferti et al studied nine patients with MM and one with PCL and found a chromosomally abnormal clone in five (50%). Most of the patients in these four studies were in the advanced stages of disease. Van Den Berghe et al studied 26 patients with untreated MM, five (19%) of whom had a chromosomally abnormal clone. The results in our study were similar—of 32 patients with untreated MM, six (18%) had an abnormal clone.

It is apparent that the incidence of chromosome abnormalities in patients with plasma cell proliferation depends on the subset studied and the presence of evolving leukemia (Table 2). The frequency of chromosomally abnormal clones identified by routine chromosome analysis was greatest among patients with advanced or resistant MM (63%) and least among patients with smoldering MM (0%). Because our sample size of five patients with PCL is small, the frequency of abnormal clones among patients with this disease (40% abnormal) may not be an accurate estimation of the true incidence of such clones among these patients. More patients with PCL need to be studied to determine the true incidence of chromosomally abnormal clones.

We are unaware of reports concerning chromosome abnormalities in patients with AL. Five of our 11 patients with AL had a chromosomally abnormal clone. Each of these patients had undergone chemotherapy prior to chromosome analysis, and ANLL eventually developed in three of them. Because the karyotype of the three patients with ANLL involved abnormalities of chromosome 7, we suspect that the abnormal clones were associated with a leukemic process rather than with AL. The abnormal karyotype of a fourth patient lacked a Y chromosome. This anomaly may not be associated with AL either but may be a "normal" aging phenomenon. The abnormal karyotype of the fifth patient with AL involved a 14q+ chromosome. Thus, at least some patients with AL have chromosome abnormalities associated with their plasma cell proliferative process.

**Specific chromosome abnormalities in plasma cell disorders.** The limited literature on cytogenetic studies on patients with plasma cell disorders suggests that a 14q+ anomaly is the most common chromosome abnormality in MM and related disorders—it occurs in about 30% of such cases. Of our 29 patients with a chromosomally abnormal clone, 11 had an abnormality of chromosome 14. In each case, the breakpoint was at 14q32 and the anomaly seemed to originate from a translocation. In three of these patients, the 14q+ anomaly was derived from an 11;14 translocation. This was the single most common structural anomaly in our series. This same translocation has been reported in three patients with MM, in two with PCL, in four with B cell chronic lymphocytic leukemia, in four with B cell lymphoproliferative disorders, and in two with small cell lymphoma. Thus, this translocation, and especially band 14q32, may be specific for malignant B cell disorders and may be especially common in MM. Interestingly, there is now evidence that another location (14q11 to q13) on chromosome 14 may be specifically associated with certain T cell leukemias and lymphomas.

Philip recently reviewed the literature regarding chromosome abnormalities in monoclonal gammopathies and concluded that, in addition to abnormalities of chromosome 14, abnormalities of chromosomes 1 and 3 were preferentially involved. The results of our study support his data regarding chromosomes 1 and 14. Twelve of our patients had an abnormality of chromosome 1 and one had two anomalies of chromosome 1: six patients had deletions, six had translocations, one had an isochromosome, and one had a duplication of part of the long arm. Although these abnormalities were different among our patients, in most instances the breakpoints involved the pericentromeric region of chromosome 1 in either band 1p11 or band 1q11. Perhaps one or both of these sites are important in either the origin or the progression of MM. Similar chromosome 1 abnormalities have been associated with other types of malignant neoplasms.

Abnormalities of chromosome 11 have not been strongly linked with plasma cell disorders, but in our study nine patients had an abnormality of chromosome 11. Seven patients had a translocation and two patients had a deletion. In four patients the translocation breakpoint involved the long arm in either band 11q13 or band 11q23: three were derived from an 11;14 translocation and one from an 11;13 translocation. In the three other translocations and the two deletions, the breakpoints were on the short arm.

Bands 11q13 and 11q23 are recognized constitutional fragile sites that occur in some normal people and are inherited in a mendelian fashion. Recently, Yunis reported finding a fragile site at 11q13 in normal cells from one of two patients with lymphoma associated with an 11;14 translocation. He suggested that because of the fragility of this site, it might be predisposed to the formation of chromosome abnormalities. Although this fragile-site hypothesis might explain the 11q13 breakpoint, it does not readily explain the chromosome 14 breakpoint. Nevertheless, this observation could be important and should be further investigated. Unfortunately, all of our patients with 11q13 breakpoints died before we could investigate the possibility of their having any fragile sites.

Manolova et al found a 17p+ in four consecutive patients with MM and suggested that this anomaly might be
specifically associated with MM. They were unable to establish the origin of the extra chromatin in any case, but the size of the abnormal 17p arm was about twice normal. In the series of ten patients with MM studied by Elemer et al,4 one patient had a similar 17p+ chromosome. In our study, one patient had a 17p+ chromosome similar to that reported by Manolova et al.23 Our patient had MM and eventually developed ANLL. Thus, we cannot be certain whether this abnormal clone was associated with MM or ANLL.

Chromosome abnormalities in plasma cell disorders and leukemia. There are 25 reported patients with both MM and acute leukemia who have had chromosome studies.1,41-50 The abnormal karyotypes in most of these patients were hypodiploid and involved loss or structural abnormalities of either chromosome 5 or 7. These chromosome abnormalities are the type that Rowley et al21 and Pedersen-Bjergaard et al22 associated with therapy-associated leukemia.

In our study, ten patients had been treated for MM or AL and had cytopenia at the time of chromosome analysis. Six of these patients eventually developed ANLL, and three had a myelodysplastic syndrome. The tenth patient died with cytopenia of unknown cause. We found only normal metaphases in one of the patients who developed ANLL, but clones were found with an anomaly of either chromosome 5 or 7 in four other patients with ANLL. The other patient with ANLL had an abnormal clone with 45 chromosomes that was lacking an X and had a 17p+ chromosome as well as a polyploid clone with many marker chromosomes. One of the patients with a myelodysplastic syndrome and the patient with cytopenia of unknown cause had a clone with monosomy 7. The karyotypes of the two other patients with myelodysplastic syndromes were only trisomy 15 and trisomy 19. There is some evidence that each of these patients may have had their myelodysplastic syndrome prior to therapy, but we cannot be sure. Interestingly, in one patient (patient No. 9) the karyotype of the abnormal clone involved both a 14q- chromosome and a structurally abnormal chromosome 5. Thus, this cell line contains anomalies characteristic of both MM and leukemia. In the other cases, the abnormal clones were more characteristic of leukemic processes than of plasma cell disorders.

Clinical usefulness of cytogenetic studies. The differences among the survival curves for our patients according to their cytogenetic classifications (AA, AN, and NN) were statistically significant. These results indicate that patients with a chromosomally abnormal clone have a poorer prognosis than those with normal mitotic cells when studied with routine chromosome analysis. Two other reports based on retrospective studies that involved small numbers of patients have attempted to correlate patient survival with a chromosomally abnormal clone. Liang et al2 investigated six chromosomally abnormal and 12 chromosomally normal patients and noted that most of the chromosomally abnormal patients died shortly after chromosome analysis. Philip et al3 studied the survival of 16 patients with a chromosomally abnormal clone and nine with normal chromosomes. They found no statistical differences in survival among these patients but did note that most of their patients had advanced disease and that overall survival was only for a few months in both groups.

We believe that cytogenetic studies are useful for all patients with newly diagnosed MM or AL because they can help to identify patients who have a poor prognosis. For example, none of the five patients in our study who had newly diagnosed MM and a chromosomally abnormal clone appeared to have an aggressive myeloma; but three of these patients did have an aggressive myeloma and died within 12 months. The two other patients are still alive: one had a possibly benign chromosome abnormality (−Y), which may be a normal aging phenomenon,23 and has survived four months. The other patient has survived 13 months but now has resistant MM. Another patient with newly diagnosed MM and an abnormal clone had cytopenia at the time of diagnosis; this patient died within two months, and the cytopenia was attributed to an evolving preleukemia.

Cytogenetic studies are helpful for distinguishing patients with a plasma cell proliferation who have cytopenia because of an evolving therapy-associated leukemia from those with a progressive bone marrow infiltration of plasma cells. Because this information can be helpful in the clinical management of such patients, chromosome studies are helpful when patients develop cytopenia of unknown cause. Our results and those of others suggest that patients with evolving therapy-associated leukemia are often characterized by either loss of or alteration in the structure of chromosomes 5 or 7 or both.41-50 In contrast, our results suggest that patients with active MM are characterized by different abnormalities that often involve chromosomes 1, 11, and 14.

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REFERENCES


The clinical significance of cytogenetic studies in 100 patients with multiple myeloma, plasma cell leukemia, or amyloidosis

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