Duplication of Part of the Long Arm of Chromosome 1 in Marrow Cells of a Treated Case of Myelomatosis

By A. I. Spriggs, J. M. Holt, and Jean Bedford

In a case of classical myelomatosis treated with melphalan, a clone of cells with a chromosomal abnormality was found in the bone marrow during remission. There was good reason to think that the hematopoietic cells, rather than plasmacytoma cells, were implicated. Although the clone persisted, no evidence of leukemia developed over a period of observation of 2 yr. The anomaly was interpreted as a duplication of part of the long arm of chromosome 1, which appeared to involve the segment q21 to q31.

LEUKEMIC CLONES developing in the course of treatment of myeloma show various chromosome anomalies. Consequently, it might be thought that the development of a karyotypically abnormal clone in the marrow during melphalan treatment would be a sign of incipient leukemia. In the following case an abnormal clone persisted for 2 yr without any evidence of leukemia developing.

CASE HISTORY

Mrs. H. L. (R.I. 46 44 06), born 1890, first complained of pain of girdle distribution in the back and lower abdomen in 1967. The pain became increasingly severe and disabling, and in 1969 multiple myeloma was suspected because the sedimentation rate was 107 mm in 1 hr. A radiographic survey of the skeleton showed extensive areas of bone lysis in spine, pelvis, rib cage, and skull, and the bone marrow was infiltrated with atypical plasma cells of myeloma type. Other investigations were as follows: Hb, 12.6 g/dl; WBC 8.3 x 10^9/liter; platelets 258 x 10^9/liter; E.S.R. 90 mm in 1 hr; calcium 2.35 mmole/liter; total serum proteins 92 g/liter (albumin 30); sharply defined band in gamma area on cellulose acetate electrophoresis. Immunelectrophoresis showed a myeloma protein of the IgGk type (IgG 39, IgA 1.55, IgM 0.3 g/liter). No Bence-Jones protein in the urine.

Treatment with intermittent courses of melphalan with prednisolone (melphalan, 10 mg daily, and prednisolone, 40 mg daily for 7 days) was begun and by the end of the first year, after seven courses had been completed, she no longer complained of pain and was living a normal active life for a lady in her 80th year. The bone marrow contained only a small number of plasma cells, and the concentration of myeloma protein had fallen from 39 to 9 g/liter. The patient's subsequent health during the 41/2-yr period August 1970 to February 1975 remained good, except for a tendency to infection of the urinary tract. By February 1975, she had completed 24 courses of melphalan and prednisolone, though the last 8 courses were for 4 days only, to avoid clinically important leukopenia. During the period of remission, the concentration of myeloma protein ranged between 5 and 11 g/liter, but there was no recovery in the concentration of IgA and IgM. The marrow persistently showed a small number of atypical plasma cells.

The patient was last seen in February 1975, at which time she was well and denied pain or recent infection. Blood count was normal as follows: Hb 12.3 g/dl; WBC 4.2 x 10^9/liter (75°, neu-
trophils); platelets 150 x 10^9/liter; E.S.R. 14 mm in 1 hr. In October 1974 serum protein measurements were total 66 g/liter (albumin 46), IgG myeloma protein 6.0, IgA 0.6, and IgG 1.0 g/liter.

She died suddenly at home in April 1975, and though no autopsy was carried out, the cause of death was thought by her family practitioner to be myocardial infarction.

**CYTOGENETIC FINDINGS**

Chromosome preparations were made from marrow samples of Feb. 14, 1973; Sept. 26, 1973; and March 6, 1974—also blood cultures of June 25, 1973; Oct. 10, 1974; and Nov. 20, 1974.

Marrow was collected in 5 parts of Eagle's medium with 2 parts of human serum, heparinized, and containing colcemid (2 parts per million). Air-dried spreads were made after standard fixation, without any prior incubation. G-bands were studied using a trypsin-Giemsa technique. All marrow samples showed a majority of metaphases to be normal except for a consistent anomaly. The cells were 46 XX, with one of the No. 1 chromosome pair replaced by a long marker (Fig. 1). This marker was interpreted as a No. 1 with a duplication of part of the long arm, giving the karyotype 46, XX, dir dup (1) (pter—q32:: q2?1—qter). Bands 1q2 and 31 were therefore duplicated (Fig. 2). A probable origin for this duplication, by chromatid exchange, is illustrated in Fig. 3. Any other explanation would involve greater complexity.

**Table 1**

<table>
<thead>
<tr>
<th>Date</th>
<th>Marrow Cells Scored</th>
<th>Marker Present</th>
<th>72-hr Blood Culture</th>
<th>Mitogen</th>
<th>Cells Scored</th>
<th>Marker Present</th>
</tr>
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<tr>
<td>Feb. 14, 1973</td>
<td>78</td>
<td>62</td>
<td>0</td>
<td>PHA</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>June 25, 1973</td>
<td>18</td>
<td>12</td>
<td>0</td>
<td>PHA</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>Sept. 26, 1973</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>PHA</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Mar. 6, 1974</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>PWM</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Oct. 10, 1974</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>PWM</td>
<td>39</td>
<td>1</td>
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<tr>
<td>Nov. 20, 1974</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>PWM</td>
<td>39</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 1. Pairs of chromosomes from six different bone marrow cells of Feb. 14, 1973, stained by the trypsin–Giemsa method. In each pair the A.1 chromosome is shown on the left, and the marker chromosome on the right.
In the first marrow sample (Feb. 14, 1973), 62 out of 78 cells scored showed the marker. In the two subsequent marrow samples, the marker was seen, respectively, in 12 of 18 and in 11 of 15 cells scored. In the three stimulated blood cultures, one cell showing the marker was found on one occasion.

Since myeloma cells were scarce in all marrow samples, and since there were frequent dividing myeloid cells of normal morphology, it was inferred that hemopoietic cells carried the anomaly.
DISCUSSION

The hematologic findings in this case do not fit with the supposition that the cells with the chromosome anomaly were myeloma cells, nor that they were of lymphoid derivation at all. This case is therefore to be separated from those where dysproteinemia is associated with a long marker chromosome in the lymphocytes or plasma cells. The long marker chromosomes described from the lymphoid or plasma cells in Waldenström’s disease are in any case usually different. In most cases, these have been of the same length as a No. 1, with an altered centromere position consistent with a pericentric inversion, as suggested by Patau.1

However, in two cases of dysproteinemia a chromosome has been seen, from cultured lymphocytes, which might be similar to ours;2 also from lymph nodes in several cases of malignant lymphoma3-5 and mycosis fungoides,6 and cell lines cultured from Burkitt’s tumor.7 (This chromosome was named by Miles7 the RM-1 or Madison marker). Similar markers are known from the bone marrow in polycythemia,8 and from direct preparations of carcinoma of the colon.9 None of the abovementioned studies included chromosome banding. Other possible examples are scattered through the literature of chromosome changes in human cancer, reported before the introduction of banding methods.

More recently, Granberg and colleagues10 have reported a carcinoma of the stomach in which, besides other anomalies, banded cells from pleural fluid showed a No. 1 chromosome which appeared to have a similar duplication to that found in our case. Another is seen in Fig. 2 of Hayata et al.,11 from a case of chronic granulocytic leukemia in blast crisis. Another possibly similar rearrangement is seen, along with others, in the marrow of a case of myeloma (treated with cyclophosphamide) described by Philip and Drivsholm;12 these were assumed to be tumor cells.

The anomaly described here seems likely to be one of those “preferred” chromosome changes that can confer a selective advantage upon the cells which carry it. Certain other abnormalities of the No. 1 chromosome are described in myeloproliferative disorders, involving trisomy for at least the long arm,13 and this may perhaps result in an analogous growth advantage. Possibly in the present case a myeloid cell line was generated in which the duplicated segment permitted relative resistance to chemotherapy. Evidently, the development of such a clone is not inevitably associated with neoplastic (i.e., leukemic) behavior, at least in the short term; but it may well be one of the alternative steps of a multistage process leading to neoplasia.

ACKNOWLEDGMENT

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REFERENCES

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