A t(1;19) Chromosome Translocation in Three Cases of Human Malignant Melanoma

Annette H. Parmiter, Gloria Balaban, Meenhard Herlyn, Wallace H. Clark, Jr., and Peter C. Nowell

ABSTRACT

Abnormalities of chromosome 1, including trisomy for all or a portion of the long arm, have been frequently reported in many cancers. Abnormalities of chromosome 19 are far less common, although a t(1;19)(q23;p13) translocation has been reported in association with pre-B-cell leukemia. We have observed a t(1;19)(q12;p13) translocation in three cases of advanced melanoma, with the translocation chromosome representing an extra dose of 1q in each instance. The breakpoint on 1q was within the centromeric heterochromatin, proximal to the site in pre-B-cell leukemia, but the breakpoint on 19p appeared identical. The gene for human insulin receptor has recently been mapped to this region of chromosome 19 (p13.2-13.3). This gene shares structural and sequence homologies with the epidermal growth factor receptor (erb-B oncogene) and members of the src family of oncogenes, suggesting that alterations in the insulin receptor, resulting from chromosomal translocation, could lead to a role in tumorigenesis. The present findings may permit this possibility to be examined in a neoplasm of neuroectodermal origin.

INTRODUCTION

Specific chromosomal translocations have been shown to be associated with certain types of human cancers (1, 2). It has been hypothesized that these nonrandom karyotypic changes involve sites in the genome where genes important in carcinogenesis are located ("proto-oncogenes") (3). This hypothesis has found support from studies of several hematopoietic tumors (e.g., Burkitt’s lymphoma and chronic granulocytic leukemia) where specific chromosome translocations have been shown to result in altered function of the c-myc and c-abl proto-oncogenes, respectively (4, 5).

Nonrandom involvement of certain chromosomes, particularly Nos. 1, 6, and 7, has been observed in human malignant melanoma (6–9). The region of chromosome 1 most commonly involved is 1p11–p22, suggesting that a gene important in the development of this neoplasm is located within the proximal portion of 1p. We report three cases of advanced melanoma with a t(1;19)(q12;p13) translocation. Since the breakpoint is not within the region 1p11–p22 previously reported in melanoma, a different mechanism is probably responsible for the selective advantage apparently conferred by this chromosomal rearrangement.

MATERIALS AND METHODS

We have obtained chromosomal data from cell lines or direct preparations of 28 cases of advanced human malignant melanoma (9). The cell lines were treated with colchicine for 30 min at 37°C. After treatment with a KCl-sodium citrate hypotonic solution and standard fixation, air dried slide preparations were made for Giemsa banding (10). For direct preparations the tumor was minced to obtain a single-cell suspension, treated with colchicine for 60 min at 37°C, and processed as described above. Karyotypes were determined from a minimum of 15 counts and 3 banded karyotypes for each case.

RESULTS

The chromosome findings in the three cases reported are summarized in Table 1. Cells from the primary lesion of case WM 39 were first examined at passage 64 in culture. The modal number was hypotetraploid, and all karyotypes had a t(1;19)(q12;p13) translocation which resulted in an extra dose of 1q (the translocation was not reciprocal). The cells also had extra copies of chromosome 7, a 7p+ marker of undefined origin, a t(10;13)(q11;q34) translocation, and a 16q+ marker (Fig. 1). This cell line was examined on two other occasions over the course of 7 months and was karyotypically stable.

Cells from case ML793, derived from an advanced primary lesion, were first examined at passage 5 in culture. The modal number was hyperdiploid, and the t(1;19)(q12;p13) translocation (Fig. 1, inset) again did not appear to be reciprocal, resulting in an extra dose of the long arm of chromosome 1. There were variable changes in chromosome 6 and an extra copy of chromosome 7, plus other random markers. These cells were again examined at passages 11 and 41 with retention of the t(1;19) translocation and the appearance of several new alterations (Table 1).

In the third case, ML991, four metaphases were obtained from a direct preparation of a metastasis to the skin. The one cell karyotyped had 69 chromosomes including four t(1;19)(q12;p13) translocation chromosomes, (Fig. 1, inset), an extra copy of chromosome 7, a del(6)(q21), and additional undefined markers. The same markers could be identified in the three other metaphases from this preparation. A second skin metastasis, (ML991), removed at the same time, was established in tissue
Table 1
Chromosomal data from the 3 cases with the t(1;19) translocation

<table>
<thead>
<tr>
<th>Case</th>
<th>Lesion</th>
<th>Date</th>
<th>Counts</th>
<th>Modal chromosome no.</th>
<th>No. of karyotypes</th>
<th>Abnormalities of chromosome no.</th>
<th>Additional chromo- changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM39</td>
<td>Primary</td>
<td>4/84 (64)</td>
<td>34</td>
<td>85</td>
<td>5</td>
<td>+1,+t(1;19) 6q-</td>
<td>1(10;13),16q+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/84</td>
<td>16</td>
<td>85</td>
<td>3</td>
<td>+1,+t(1;19) 6q-</td>
<td>1(10;13),16q+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/84</td>
<td>21</td>
<td>85</td>
<td>2</td>
<td>+1,+t(1;19) 6q-</td>
<td>1(10;13),16q+,</td>
</tr>
<tr>
<td>ML793</td>
<td>Primary</td>
<td>6/83 (5)</td>
<td>18</td>
<td>48</td>
<td>3</td>
<td>+1,+t(1;19) 6q-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/83 (11)</td>
<td>15</td>
<td>49</td>
<td>5</td>
<td>+1,+t(1;19) 6q-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/84 (41)</td>
<td>43</td>
<td>49</td>
<td>4</td>
<td>+1,+t(1;19) 6q-</td>
<td></td>
</tr>
<tr>
<td>ML991</td>
<td>Metastasis 1</td>
<td>9/84 (direct)</td>
<td>4</td>
<td>69</td>
<td>1</td>
<td>+1,+t(1;19) del 6q21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastasis 2</td>
<td>11/84</td>
<td>52</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>8p+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/84 (5)</td>
<td>4</td>
<td>79</td>
<td>1</td>
<td>+1,+t(1;19) del 6q21</td>
<td>8p+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12/84</td>
<td>17</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>8p+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/85</td>
<td>14</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>8p+,</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, passage in culture.
** undetermined markers.

Fig. 1. Karyotype from melanoma cell line WM 39 demonstrating two der t(1;19)(q12;p13) chromosomes (arrow), as well as characteristic 7p+, 16q+, t(10;13)(11;q34) translocation and four unidentified markers. This metaphase had only 75 chromosomes due to random loss. Inset, der t(1;19)(q12;p13) chromosomes from another WM 39 cell and from the two other melanomas, ML793 and ML991, in which this rearrangement was identified.

culture and subsequently karyotyped after 2, 3, and 7 months in culture. These cells showed the same consistent alterations as the karyotype from the direct preparation, with the addition of an iso8q appearing at 7 months (Table 1).

In order to clarify the location of the breakpoint on the long arm of chromosome 1, C-banding was done on cases ML793 and ML991. In both cases, as illustrated in Fig. 2, two C-banded areas were present on the der(1;19) chromosome, apparently corresponding to the active centromere of the No. 19 and a portion of the centromeric heterochromatin of the No. 1. These findings support the conclusion from the G-banded material that the breakpoint was within the centromeric region of chromosome 1.

DISCUSSION

Frequent involvement of chromosomes 1, 6, and 7 has been reported in human malignant melanoma (6–9). This report of three cases of a t(1;19) translocation, however, apparently represents the first example of a nonrandom translocation in this
ably represents the centromere of chromosome 19, with the lower density being the translocated portion of the centromeric heterochromatin of chromosome 1.

The breakpoint in chromosome 1 does not correspond to previous descriptions of abnormalities in chromosome 1 in melanoma, which have been noted primarily in the region p11–p22 (9). The breakpoint on 1q apparently does not involve the site of any active gene, since it is within the centromeric heterochromatic region. This would suggest that a phenomenon such as the one involved in Burkitt’s lymphoma or chronic granulocytic leukemia (4, 5), where a proto-oncogene is brought into contact with “activating” sequences in other parts of the genome, is not operating in these melanoma cases.

In all three cases, the t(1;19) translocation appeared not to be reciprocal, thus resulting in extra dosage of 1q. This phenomenon has been observed in many types of hematopoietic and nonhematopoietic tumors (1, 2, 12). It has been postulated that an extra dose of one or more unidentified genes in the midregion of 1q (q21–32) can lead to a selective growth advantage in many types of cells (12). The decreased number of copies of the short arm of chromosome 1 may also be important. In reports of human solid tumors, investigators have most often described seeing an extra chromosome 1 with most of the short arm deleted (13–15). Similar observations have been made in various hematopoietic neoplasms, suggesting that an imbalance between genes on 1p and on 1q may be particularly significant.

Cytogenetic abnormalities involving chromosome 19 have been relatively uncommon. Recently, a t(1;19) translocation has been described in pre-B-cell leukemia (16–20) as well as in small cell carcinoma of the lung (21) and non-Hodgkin’s lymphoma (28). The reported breakpoints for chromosome 1 ranged from 1 q21–q25, distal to the breakpoint in the present report, but the site at which the breakpoint at 19 p13 is probably the same. We have also noted translocations to 19 p13 with different donor chromosomes in myeloid preleukemia (22) and there have been scattered reports of a similar finding in other leukemias and nonhematopoietic cancers (23). Taken together, these observations suggest that 19 p13 is the site of a gene important in carcinogenesis.

Recently, the gene for the human insulin receptor has been mapped to this region (24). Since this gene shares structural and sequence homologies with the epidermal growth factor receptor (the erb-B oncogene) and with the products of the src family of oncogenes, it has been postulated that it may also act as an oncogene (24). Rearrangement of this gene may alter its normal receptor function and thereby contribute to neoplastic proliferation.

A fragile site has also recently been mapped to chromosome 19 and reported as 19 q13 (25). Given the difficulty of proper arm assignment in chromosome 19, this locus could actually be at 19 p13, the site involved in the breakpoints described above. The significance of the common fragile sites in the genome is still unknown, but it has been speculated that they may play a role in oncogenesis (26, 27).

Melanoma cells carrying the particular t(1;19) translocation observed here may prove useful for exploring various questions concerning 19p and 1q at the molecular level.

REFERENCES

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