Specific Cytogenetic Changes in Ovarian Cancer Involving Chromosomes 6 and 14

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ABSTRACT

Cytogenetic studies were performed in 12 papillary serous adenocarcinomas of the ovary. Of the more than 19 clonal structural chromosome abnormalities observed in these cancers, 6q− and 14q+ were found to be the most frequent. Both markers coexisted in the cells of eight cases; in the other four cases, either a 6q− or 14q+ was present. In at least six cases, the additional segment on the long arm of chromosome 14 appeared to originate, on the basis of the chromosomal quantity and fluorescence pattern, from the missing part of chromosome 6. This suggested that the 6q− and 14q+ markers had arisen as a result of a reciprocal translocation at Bands q21 and q24, respectively, i.e., t(6;14)(q21;q24). However, it is uncertain in the remaining six cases whether an identical type of translocation was responsible for the formation of the markers. Thus, abnormalities involving chromosomes 6 and 14 seem to be specifically associated with papillary serous adenocarcinoma of the ovary.

INTRODUCTION

Papillary serous adenocarcinoma of the ovary represents a malignant form of serous cystadenoma in which all grades of pathological transitions have been observed, ranging from a picture of a benign papillary serous cystadenoma to almost solid papillary masses of adenocarcinoma.

In spite of the fact that ovarian cancers are not rare in women, only 25 cases have been examined by chromosome banding techniques, the great majority being metastatic tumors (1, 2, 4, 7, 14). No attempt was made in these studies, however, to subdivide the material according to histological types. This is compounded by the extremely complicated karyotypic rearrangements found in most ovarian cancers, necessitating further detailed and stringent cytogenetic analyses before the chromosomal findings could be interpreted properly. So far, the nonrandom involvement of chromosome 1 in structural changes has been reported (1, 2, 4, 7, 14). A similar involvement of chromosome 1, however, has been reported in several other human cancers besides those of the ovary (lung, cervix, and melanoma) (13). In both the ovarian and other studies, data on the complete karyotypes of the tumors were not given. The specificity of chromosome 1 involvement in ovarian cancer has not been established rigorously since comparable data on other chromosomes were not available.

The present study was undertaken in order to investigate whether any specific chromosomal abnormality is associated with ovarian cancer of the same histological appearance. The results have shown that a reciprocal translocation between chromosomes 6 and 14, which takes place most probably in a nonrandom fashion, is characteristic of serous papillary adenocarcinoma of the ovary. In accordance with previous reports, abnormalities of chromosome 1 were also frequently observed.

MATERIALS AND METHODS

In this study, chromosomes were analyzed on 12 tumor specimens which had been pathologically diagnosed as papillary serous adenocarcinomas of the ovary; they included 5 primary tumors and 7 metastatic tumors.

Cell suspensions were made by mincing and pipetting the tumor tissue in Roswell Park Memorial Institute Tissue Culture Medium 1640 containing 20% fetal calf serum and then incubating the cells for 2 days in an atmosphere of 5% CO2 in air followed by a 12-hr treatment with 0.01 µg of Colcemid per ml. Chromosome analysis was performed by sequential staining of the cells with conventional Giemsa and then with quinacrine mustard.

A chromosome abnormality was considered as clonal in origin when at least 2 cells from a given tumor had a similar rearrangement or when 3 cells gained or lacked the same chromosomes. When it was impossible to trace the origin of marker chromosomes reliably, they were referred to as unidentified chromosomes.

RESULTS

Cytogenetic studies were performed on the ovarian tumors of 12 patients. The pertinent clinical and pathological data are shown in Table 1. Prior to the chromosome examination, 4 patients had received chemotherapy (Cases 1, 6, 11, and 12) and/or radiation therapy (Cases 1 and 12). The remaining 8 patients had not been treated with cytotoxic agents or radiation therapy prior to the initial cytogenetic analysis.

Although the tumor tissues provided dividing cells (in culture) in varying numbers and their chromosomes were fuzzy, all 12 cases described herein were successfully analyzed by banding. All tumor specimens were found to have chromosomally abnormal cells. The modal chromosomal number was hypodiploid in 3 cases, pseudodiploid in one case, hyperdiploid in one case, and near triploid in 7 cases (Table 2). Poorly differentiated carcinoma cells were seen in 3 of 4 cases in which the modal number was hypodiploid or pseudodiploid and in only 2 of 8 cases in which the modal number was hyperdiploid or near triploid.

Although all of the 12 ovarian tumors had complex karyotypes with many rearranged chromosomes, a total of 51 cells was successfully karyotyped by Q-banding. A comparison of

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the karyotypes based on 3 or more cells in each case disclosed the preferential involvement of chromosome 1 as a chromosomal gain and the X chromosome as a chromosomal loss. Thus, the former was observed in 6 cases and the latter in 9 cases.

Nineteen kinds of structural chromosome abnormalities were identified as of clonal origin (Table 2); among them, 6q− and 14q+ were most frequent. Each marker was observed in 10 cases, respectively. Both markers coexisted in 8 cases; there was no case without such markers. Of the 51 karyotyped cells from the 12 cases, 26 exhibited both markers. Only 5 cells showed neither marker. Either a 6q− or 14q+ marker was noted in the remaining 20 cells. The incidence of cells possessing both markers was 33.3% (7 of 21) in poorly differentiated, 72.7% (16 of 22) in moderately differentiated, and 37.5% (3 of 8) in well-differentiated carcinomas and thus seemed not to be related to the degree of histological differentiation. However, the frequency of cells without the 6q−

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Stage</th>
<th>Histological differentiation</th>
<th>Tissue for chromosome examination</th>
<th>Therapy before the chromosomal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>III</td>
<td>Moderately differentiated</td>
<td>Metastatic tumor to the gastrocolic ligament</td>
<td>Radiation, chemotherapy (actinomycin D, Cytoxan, and 5-FUra)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>III</td>
<td>Poorly differentiated</td>
<td>Metastatic tumor to the omentum</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>IV</td>
<td>Poorly differentiated</td>
<td>Metastatic tumor to the omentum</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>III</td>
<td>Moderately differentiated</td>
<td>Primary tumor</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>III</td>
<td>Moderately differentiated</td>
<td>Primary tumor</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>III</td>
<td>Poorly differentiated</td>
<td>Metastatic tumor on the abdominal wall</td>
<td>Chemotherapy (MTX, Cytoxan and cis-DDP)</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>III</td>
<td>Well differentiated</td>
<td>Metastatic tumor to the omentum</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>III</td>
<td>Poorly differentiated</td>
<td>Primary tumor</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>III</td>
<td>Moderately differentiated</td>
<td>Primary tumor</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>III</td>
<td>Moderately differentiated</td>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>III</td>
<td>Poorly differentiated</td>
<td>Pleural effusion</td>
<td>Chemotherapy (Cytoxan, cis-DDP, and Adriamycin)</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>III</td>
<td>Well differentiated</td>
<td>Primary tumor</td>
<td>Radiation, chemotherapy (5-FUra, Cytoxan, Adriamycin, and cis-DDP)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>No. of cells examined</th>
<th>Chromosome no.</th>
<th>Chromosome gain</th>
<th>Chromosome loss</th>
<th>Clonal chromosome abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56-63 (60)</td>
<td>1, 6, 16, 18, 20</td>
<td>22, X</td>
<td>6q−, 6q−, 1p−, 14q+, 6q+</td>
</tr>
<tr>
<td>2</td>
<td>27-75 (68)</td>
<td>3, 9</td>
<td></td>
<td>6q−, 14q+</td>
</tr>
<tr>
<td>3</td>
<td>30-83 (41)</td>
<td>5, 7, 9, 18, 19, 20, X</td>
<td>3q+, 3p+q+, 1p−, 1q−, 6q−, 11q−</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>45-64 (62)</td>
<td>1, 5, 10, 21, 22, 22, 11, X</td>
<td>1p−q−, 6q−, 10q−, 14q+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>29-80 (34, 36)</td>
<td>3, 9, 10, 13, 14, 15, 17, 18, 21, 22, X</td>
<td>6q−, 14q+, 1q−, 1p−</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>38-87 (46)</td>
<td></td>
<td></td>
<td>6q−, 14q+, 1p−q−, 3p+q+</td>
</tr>
<tr>
<td>7</td>
<td>49-66 (62)</td>
<td>1, 1, 13, 14</td>
<td></td>
<td>6q−, 14q+, U</td>
</tr>
<tr>
<td>8</td>
<td>31-83 (41)</td>
<td>3, 4, 7, 9, 10, 11, 15, 18, 19, X</td>
<td>1p−q−, 1q−, 13q+, 6q−, 14q+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>41-110 (59)</td>
<td>1, 2</td>
<td>X</td>
<td>13q+, 14q+</td>
</tr>
<tr>
<td>10</td>
<td>58-69 (68)</td>
<td>8, 10, 12, 14, 15, 16, 16, 17, 17, 22</td>
<td>X</td>
<td>1p−q−, 1p+q−, 4q−, 6q−, 8q−, 10q+, 14q+, U, &amp; U2</td>
</tr>
<tr>
<td>11</td>
<td>61-69 (68)</td>
<td>1, 2, 3, 8, 9, 10, 10, 13, 13, 14, 16, 17, 18, 21, 22, 22, X</td>
<td>6, 7, 11, 19, X</td>
<td>1p+q+, 1p−q−, 2q+, 3q+, 4q+, 12q+, 14q+, 6p+, U(iso-17q?)</td>
</tr>
<tr>
<td>12</td>
<td>40-54 (50)</td>
<td>1, 3, 12, 20</td>
<td>14, 16, 16, X</td>
<td>1p−, 6q−</td>
</tr>
</tbody>
</table>

* 5-FUra, 5-fluorouracil; MTX, methotrexate; cis-DDP, cis-diaminedichloroplatinum (ii).

** Numbers in parentheses, modal number.

* U, unidentified chromosome.
marker was 52.4% (11 of 21) in the first group, 27.3% (6 of 22) in the second group, and 12.5% (1 of 8) in the last group, indicating some correlation with histological type.

In 6 of the cancers (Cases 1, 2, 4, 6, 8, and 10), the additional segment on the long arm of chromosome 14 appeared to be very similar in size and banding pattern to the segment missing from chromosome 6. This suggested strongly that the 6q- and 14q+ markers had arisen as a result of a reciprocal translocation at q21 and q24, respectively, i.e., t(6;14)(q21;q24) (Fig. 1). However, it was uncertain in the remaining 6 cases whether an identical type of translocation was responsible for the formation of the markers (Fig. 2). Thus, the banding pattern of the 6q— markers in 3 cases (Cases 3, 5, and 7) showed that the break point seemed not to correspond to q21. In Cases 5 and 7, the additional segment of the 14q+ marker did not match in quantity the deleted portion of the 6q— marker. Moreover, in Cases 9 and 11, the origin of the translocated segment on chromosome 14 could not be identified. In these cases, it is possible that a more complex translocation, involving chromosomes other than 6 and 14 and affecting the nature of the translocation and bands involved, may have occurred.

Other chromosome abnormalities were noted as well; except for those discussed above, no common markers were found among the cases. These consisted of 13q+, 3p+q+, and 3q+ markers, each noted in 2 cases, and others were observed in one case each. The exception was the involvement in 9 cases of chromosome 1 in structural rearrangements. Four types of abnormalities (1p—, 1q+, 1p—q+, and 1p+q—) were identified. Each was observed in 4, 3, 5, and 2 cases, respectively.

**DISCUSSION**

The observations made in the present study indicate that the involvement of chromosomes 6 and 14 in a specific translocation rearrangement [t(6;14)(q21;q24)] is characteristic of the cells from papillary serous adenocarcinoma of the ovary. The 6q— and 14q+ markers probably originate through a reciprocal translocation. However, the break point of the 6q— marker seemed not to be identical in some cases, and hence, the additional segment on the 14q+ marker did not match in quantity with the deleted portion of the 6q— marker in 2 cases. These observations raise some doubt about the assumption that the markers are produced by identical mechanism in all cases. However, several explanations are possible: (a) further complex rearrangements might have occurred secondarily in the markers during the process of tumor progression after the t(6;14) involving identical break points had occurred in all cases; (b) as in other specific translocations, e.g., t(9;22) in chronic myelocytic leukemia and t(8;14) in Burkitt lymphoma (8, 16), a tandem t(14;14) in ataxia telangiectasia (6, 9), and translocation involving chromosome 14 in a substantial percentage of malignant lymphomas (3, 5). Our observations suggest that a t(6;14) is common in one type of ovarian adenocarcinoma. However, it remains unknown whether this type of translocation plays a role in the genesis of the oncogenic process or merely endows the cell with growth advantages.

Karyotypes have been described in a total of 25 cases of ovarian tumors (1, 2, 4, 7, 14) although some cases showed morphological characteristics that are different from those of serous papillary adenocarcinoma. Chromosome 1 was involved most frequently in rearrangements with different types of break points. The present results also confirmed chromosome 1 involvement in 9 of 12 cases. This relatively high frequency of chromosome 1 abnormalities is not due simply to its length, inasmuch as chromosome 2 of comparable length is involved in few rearrangements. However, it remains to be determined whether the abnormalities of chromosome 1 are specifically associated with ovarian carcinomas since the nature of the segments involved in the deletions was not consistent.

It remains unknown whether the t(6;14) constitutes a critical change in a cell with identical morphology or in a particular malignant cell of the ovary, which may then have a variety of appearances. 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 correlation between certain chromosome rearrangements, pathogenesis, and clinical course of ovarian tumors.

Although the part that ploidy plays in a tumor is not entirely clear, the present results are evidently at variance with those of a previous report (15). The latter authors suggested that well-differentiated tumors tend to have a modal chromosome number in the diploid range and to have sharper single modes, whereas poorly differentiated tumors had modes in the triploid range. Hypodiploid cells were assumed to originate either from chromosome 14 translocated onto chromosome 14 might be specifically associated with ovarian papillary serous adenocarcinoma, since the distal ones were consistently involved in rearrangements, except in Cases 9 and 11. However, further studies are necessary in order to provide information about the exact mechanism which produces the 6q— and 14q+ markers in cells from serous papillary adenocarcinoma of the ovary.
REFERENCES


Fig. 1. Partial karyotypes of Q-banded cells from Cases 1, 2, 4, 6, 8, and 10. Comparison of the 6q− and 14q+ markers suggests that the extra material on the long arm of chromosome 14 corresponds to the deleted material of chromosome 6, i.e., t(6;14)(q21;q24).

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Fig. 2. Partial karyotypes of Q-banded cells from Cases 3, 5, 7, 9, 11, and 12. The banding pattern of the 6q- markers in 3 cases indicates that the break point on chromosome 6 did not occur at Band q21.

Fig. 3. Q-banded karyotype of a cell from Case 1. These are extra in chromosomes 1, 2, 6, 11, 12, 15–18, 20, and 21 and a loss in chromosomes 4, 5, 22, and X. The karyotype contains 7 kinds of structural abnormalities (1p-, 1p-q-, iso-9q, 11p-, 6q+, 6q-, and 14q+). Arrows. 6q+, 6q-, and 14q+ marker chromosomes. The 14q+ chromosome is the result of a translocation with 6q-, i.e., t(6q-;14q+).
Fig. 4. Q-banded karyotype of a cell from Case 1. These are extra in chromosomes 1, 6–8, 10, 12–16, 18, 20, and 21 and a loss in chromosomes 22 and X. The karyotype contains 4 kinds of structural abnormalities (6q+, 6q−, 14q+, and iso−16q) and one unidentified marker (U1). Arrows indicate 6q−, 6q+., and 14+ marker chromosomes. The 14q+ chromosome is the result of a translocation with 6q−, i.e., t(6q−;14q+).
Fig. 5. Q-banded karyotype of a cell from Case 12. These are extra in chromosomes 1, 2–4, 12, and 20 and a loss in chromosomes 14 and 16. The karyotype contains 2 kinds of structural abnormalities (1p− and 6q−). Arrow, 6q− marker chromosome. The break point on chromosome 6 occurred at Band q21, although a 14q+ marker was not observed in this case.
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