Clear Cell Adenosquamous Carcinoma of the Cervix

An Aggressive Tumor Associated with Human Papillomavirus-18

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**Background.** It is well recognized that adenocarcinomas and adenosquamous carcinomas of the cervix are frequently associated with human papillomavirus (HPV) -16 or -18. However, few studies have investigated associations between histologic variants of these tumors and specific types of HPV.

**Methods.** Eleven cases of cervical adenosquamous carcinoma with an unusual histologic appearance were characterized using histochemical and immunohistochemical stains. Sections were tested for the presence of HPV DNA using the polymerase chain reaction (PCR) and type specific primers for HPV-16 and -18. Clinical outcome was determined from a chart review.

**Results.** All tumors were histologically characterized by the presence of sheets of cohesive cells with prominent cell borders and a vacuolated or clear cytoplasm containing large amounts of glycogen. All tumors had focal gland formation and stained positive with mucicarmine stain. Using PCR, HPV-18 DNA was identified in all cases. The youngest patient was 24 years old and the oldest 74 years (mean, 43 years). Eight (73%) of the 11 patients have developed recurrent disease with a mean follow-up until recurrence of 9.5 months (range, 3–22 months). Seven (64%) of the 11 patients have died of their cervical tumors. Of the five patients with Stage IB disease, three (60%) have died of their cervical tumors.

**Conclusions.** A subset of invasive cervical adenosquamous carcinoma associated with HPV-18 that has a distinctive histologic appearance and an aggressive clinical course is described. The term “clear cell adenosquamous carcinoma” is proposed for this unique variant of invasive cervical carcinoma. Cancer 1995;76:1591–600.

Key words: cervical adenosquamous carcinoma, clear cell adenosquamous carcinoma, human papillomavirus type 18, histopathology.
adenosquamous carcinomas of the cervix are associated with HPV and that there is a particularly strong association between these tumors and HPV-18.8-15 Little is known, however, about associations between specific types of HPV and specific histologic subtypes of cervical adenocarcinoma or adenosquamous carcinoma.

As part of an ongoing study assessing prognostic factors for invasive adenocarcinomas, we identified a group of tumors that originally were classified as adenocarcinomas of the cervix but which appear to be a subset of adenosquamous carcinoma with a distinctive histologic appearance. These tumors have not been previously described and are characterized by cells with prominent vacuolated cytoplasm containing large amounts of glycogen that form cohesive cellular sheets. All of these tumors are associated with HPV-18, and most had an aggressive clinical course. In this paper, we present the histologic features, clinical findings, and outcome of 11 patients with these tumors and propose that the term "clear cell adenosquamous carcinoma" should be used to refer to this unique variant of invasive cervical adenosquamous carcinoma.

Materials and Methods

Patients and Statistics

As part of a histopathologic study assessing the prognostic features of invasive adenocarcinomas of the cervix, we reviewed hematoxylin and eosin-stained histologic slides from 157 cases of invasive adenocarcinoma of the cervix. These cases were obtained from the pathology files of the College of Physicians and Surgeons of Columbia University (New York, NY), M.D. Anderson Cancer Center (Houston TX), Royal Victoria Hospital (Montreal, Quebec, Canada), and St. Mary's Hospital (Manchester, United Kingdom). All cases were diagnosed between 1983 and 1993. A variable number of slides was available for histopathologic review from each case. In some instances, the patient underwent a hysterectomy and the entire cervix was available for histopathologic assessment; in other cases, the patient was treated with radiation, and only a single cervical biopsy obtained before therapy was available for review. This study was approved by the Columbia University Institutional Review Board.

Charts were reviewed for race, age, date of diagnosis, clinical International Federation of Gynecology and Obstetrics (FIGO) stage,16 clinical lymph node status, lesion size, hemoglobin level at diagnosis, treatment, cell type, grade, last date of follow-up, survival status, and recurrence using a prepared clinical data abstract form. A literature search between the years of 1974 and 1994 was performed using MEDLINE to document that this entity was not previously reported.

Histopathology and Immunohistochemical Analysis

Formalin fixed, paraffin embedded tissues were used for histologic examination. Four-micron paraffin sections were stained with either hematoxylin and eosin, periodic acid–Schiff stain with (periodic acid–Schiff-d) and without (periodic acid–Schiff) digestion with diastase, or with mucicarmine stain. For immunohistochemistry, 4-μm sections were mounted on silane-coated slides (Digene Diagnostics, Silver Spring, MD) and were stained by the streptavidin-biotin method using primary monoclonal antibodies against cytokeratin (AE1/AE3, mouse, 1:300, Boehringer Mannheim, Indianapolis, IN), vimentin (V9, mouse, 1:30, DAKO, Carpinteria, CA), carcinoembryonic antigen (CEA) (SP-651, mouse 1:200, Biogenex, San Ramon, CA), estrogen receptor (ERID5, mouse, 1:40, AMAC, Westbrrook, MA), progesterone receptor (PRI, mouse 1:1, CAS, Elmhurst, IL), and c-erbB-2 (monoclonal antibody 1, mouse, 1:10, Triton, Alameda, CA).17 Before staining, sections were treated with 0.3% hydrogen peroxide to block endogenous peroxidase activity and were incubated with normal goat serum. Sections used for identifying estrogen and progesterone receptors were treated with microwave irradiation before staining. The sections then were incubated for 18 hours at 4°C with the primary antibodies followed by treatment with biotinylated goat antimouse secondary antibody and streptavidin-biotin peroxidase complex. Finally, diaminobenzidine was applied as chromogen to develop the peroxidase reaction. With each staining reaction, a positive control consisting of tissue known to contain the relevant antigen and a negative control of normal mouse immunoglobulin G, rather than the primary antibody, was included.

Polymerase Chain Reaction

Tissues were prepared for PCR by cutting three 10-μm sections from each formalin fixed, paraffin embedded tissue block, digesting the sections with proteinase K at 60°C for 16 hours, and then separating the aqueous phase from the paraffin and undigested tissue by microcentrifugation.11 Aliquots of the aqueous phase were used for all PCR amplifications. Samples were analyzed for the presence of HPV-16 and -18 DNA using typespecific primers for the E6 and the L1 regions of these two HPV types. Two separate sets of type-specific primers were used. The sequences of the E6 region type-specific primer set were: HPV-16 positive strand 5' ACC-GAAAACCGGTAGTATAAAGC 3'; HPV-16 negative strand 5' ATAACCTGCTAATTCTGGGTTC 3';
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HPV-18 positive strand, 5' CGGTCCGGAGCCGAA-
AAGCGTGC 3'; and HPV-18 negative strand, 5' CGT-
GTTGGATCCTCAAAGCGGCC 3'. The sequences of
the L1 region type-specific primer set were HPV-16
positive strand 5' TGCTAGTGGTTTATGACGAA 3';
HPV-16 negative strand 5' ATTACTGCAACATTG-
GTAC 3'; HPV-18 positive strand, 5' AAGGATGCT-
GCACCCGCTGA 3'; and HPV-18 negative strand, 5'
CACGCACACGCTTGGCAGGT 3'.

Ten μl of aqueous sample was added to 90 μl of reaction buffer contain-
ing a final concentration of 50 mM of potassium
chloride, 4 mM of magnesium chloride, 10 mM of Tris,
ph 8.5, 200 μM of dNTP, 0.2 μM of primers and 2.5
U of Taq DNA polymerase (Perkin-Elmer Cetus Corp.,
Foster City, CA). DNA was amplified for 35 cycles using
the following parameters: denaturation for 1 minute at
94°C, reannealing for 1.5 minutes at 56°C, and exten-
sion for 1.5 minutes at 72°C for the first 34 cycles and
extension for 3.0 minutes for Cycle 35. All PCR reac-
tions contained appropriate positive and negative con-
trols. Polymerase chain reaction products were electro-
phoresed using an 8% native polyacrylamide gel and
were stained with ethidium bromide. The 11 cases in-
cluded in this series were part of a larger series of 157
tumors originally classified as cervical adenocarcinomas
that we analyzed for HPV DNA using this PCR method.

Results

HPV Typing and Histologic Features

The 11 cases of clear cell adenosquamous carcinoma de-
scribed in this series were identified as part of a histo-
pathologic review of 157 invasive cervical adenocarci-
nomas and, therefore, appeared to be relatively uncom-
mon tumors. HPV-18 DNA was detected using PCR
with both sets of type-specific primers in all 11 tumors
(Fig. 1), and all 11 had a similar histologic appearance
by analysis of routine histologic sections.

The characteristic histologic pattern of clear cell ade-
osquamous carcinoma was that of a solid neoplasm com-
posed of sheets of cohesive cells with prominent cell bor-
ders and a vacuolated or clear cytoplasm (Fig. 2a and 2b).
The sheets of vacuolated cells frequently were subdivided
by connective tissue septa, which in some cases contained
a marked lymphocytic infiltrate. This often resulted in a
lobular appearance (Fig. 3a). In some cases, large numbers
of polymorphonuclear leukocytes infiltrated the solid masses of
tumor cells. In two cases, cells in the solid areas had abun-
dant eosinophilic cytoplasm and were spindle-shaped,
suggesting an attempt at squamous differentiation. How-
ever, in none of the cases was clear-cut histologic evidence
of squamous differentiation (e.g., keratin pearls, promi-
nent intercellular bridges, or individual cell keratinization)
identified. Highly atypical tumor cells with giant nuclei
were focally present in most of the cases as were numer-
ous mitoses (Fig. 3d). The nuclei of the tumor cells tended
to be large and had considerable cell-to-cell variation in
size and shape. Although prominent nucleoli occasionally
were observed, these were not a characteristic feature.

All tumors initially were diagnosed as primary cervi-
cal adenocarcinomas. Focal gland formation was ob-
served in all cases and was pronounced in 3 (27%) of the
11 (Fig. 3c). However, in three other cases, architectural
evidence of glandular differentiation was quite minimal
and only was detected by careful review (Fig. 3b). Papil-
lary and tubulocystic areas typical of clear cell carcinoma
were absent in all cases. In no areas did the cytoplasm
assume the amphophilic appearance characteristic of
glasy cell carcinoma, nor were hobnail cells, which typi-
cally are associated with clear cell carcinomas, present. In
none of the 11 cases was adjacent cervical intraepithelial
neoplasia or adenocarcinoma in situ observed.

Histochemical and Immunohistochemical Findings

Sufficient tissue remained in the paraffin blocks after
HPV analysis to allow histochemical and immunohis-
tochemical studies in 7 of the 11 cases. These seven
cases were analyzed using standard histochemical
and immunohistochemical methods. The cytoplasm

Figure 1. Polyacrylamide gel (8%) of polymerase chain reaction
amplification products obtained using primers for the E6 region of
human papillomavirus (HPV)-16 and -18. Lane W, water control;
Lane P, HPV-18 plasmid DNA; Lanes 1-11, DNA extracted from
cases 1-11; M: molecular weight markers.

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of the vacuolated cells contained large amounts of glycogen that stained positively with periodic acid-Schiff stain and was removed by digestion with diastase (Fig. 4a and 4b). Mucicarmine stains demonstrated intracellular mucin in all cases. In most, the mucicarmine staining was focal and weak, but in several, it was more pronounced (Fig. 4c and 4d). The immunohistochemical findings are summarized in Table 1. In all cases, strong cytokeratin reactivity was present in the cytoplasm of the majority of the tumor cells (Fig. 5a). Carcinoembryonic antigen also was demonstrated in all cases, but CEA staining was more focal than that observed for cytokeratin (Fig. 5b). In all seven cases, the tumor cells lacked vimentin. Although immunoreactivity for estrogen and progesterone receptors was detected using a streptavidin-biotin immunohistochemical method in cells within the stroma, the tumor cells were uniformly estrogen and progesterone receptor negative with this method. Similarly, no immunoreactivity for c-erbB-2 was detected in the seven tumors using a streptavidin-biotin immunohistochemical method (Table 1).
Figure 4. Periodic acid–Schiff stain either before (A) or after (B) diastase digestion. Intracellular mucin could be identified using the mucicarmine stain (C and D) (objective magnification ×40).

**Clinical Findings and Course**

The clinical findings and course of the 11 patients are summarized in Table 2. The youngest patient was 24 years of age and the oldest was 74 years of age (mean age, 43 years). Five of the women were white, three were African American, and three were Hispanic. Five of the tumors were classified as clinical Stage IB, one as Stage IIA, two as Stage IIB, and two as Stage IIIB. One of the tumors was unstaged. Tumor size ranged from 3.0–8.0 cm (mean size, 5.7 cm) and lymph node metastases were found in 3 (27%) of the 11 cases. One of the five patients with Stage IB disease was treated with radical hysterectomy alone, and two were treated with radiation therapy alone. The other two patients with Stage IB disease underwent radical hysterectomies that were followed by radiation therapy, and one was also treated with a course of chemotherapy. The six patients with higher stage or unstaged disease all were treated with radiation therapy either alone (n = 3) or a combination of radical hysterectomy (n = 1) or chemotherapy (n = 2).

Eight (73%) of the 11 patients developed recurrent disease with a mean follow-up until recurrence of 9.5 months (range, 3–22 months). Seven (64%) of the 11 patients died of their cervical tumors. Survival in these seven ranged from 8–30 months (mean survival, 16.8 months). As of this writing, three (27%) of the patients...
Table 1. Histochemical and Immunohistochemical Characteristics of Clear Cell Adenosquamous Carcinoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>PAS</th>
<th>PAS-d</th>
<th>Mucicarmine</th>
<th>Cytokeratin</th>
<th>Vimentin</th>
<th>CEA</th>
<th>Estrogen receptor</th>
<th>Progesterone receptor</th>
<th>cerb B-2</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+</td>
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<td>-</td>
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<td>5</td>
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<td>+</td>
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<td>-</td>
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<td>6</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>+++</td>
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<td>9</td>
<td>+</td>
<td>-</td>
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<td>+++</td>
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<td>-</td>
<td>+</td>
<td>-</td>
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</tr>
</tbody>
</table>

PAS: periodic acid Schiff stain; PAS-d: periodic acid Schiff stain after diastase digestion; CEA: carcinoembryonic antigen; -: no reactive cells; +: less than 1/3 of tumor cells are reactive; ++: 1/3-2/3 of tumor cells are reactive; +++: more than 2/3 of tumor cells are reactive.

Discussion

These 11 carcinomas of the cervix appear to comprise a new histopathologic entity not previously reported, which we have termed clear cell adenosquamous carcinoma. In our opinion, the formation of a new histopathologic category for these tumors is justified because all 11 cases have a unique and distinctive histologic appearance, all are associated with HPV-18, and, most importantly, as a group, these tumors were associated with an aggressive clinical course.

The primary site for all 11 tumors was thought to be the cervix. This interpretation was based on the presence of a cervical tumor mass and the lack of endometrial involvement as determined from either a hysterectomy specimen obtained at the time of radical surgery or from endometrial curettages obtained at the time of surgical staging. An additional finding supporting the endocervical origin, as opposed to an endometrial origin, was the lack of staining for the intermediate filament vimentin and the focal positivity for CEA observed in all cases for which blocks were available for immunohistochemical analysis. Vimentin is detected in approximately 60% of invasive adenocarcinomas of the endometrium but is usually absent in primary endocervical adenocarcinomas. Conversely, staining for CEA is relatively uncommon in invasive adenocarcinomas of the endometrium but often is observed in primary endocervical adenocarcinomas.

All of the tumors in this series were architecturally poorly differentiated. Most contained regions composed of poorly differentiated cells lacking the clear or vacuolated cytoplasm characteristic of clear cell adenosquamous carcinoma. To be classified as a clear cell adenosquamous carcinoma, we required that at least 70% of the tumor be composed of sheets of cells with vacuolated or clear cytoplasm. We classified these tumors as adenosquamous carcinomas rather than undifferentiated carcinomas for two reasons. First, all 11 cases had foci of glandular formation by analysis of routine hematoxylin and eosin-stained sections. The recent Armed Forces Institute of Pathology (AFIP) and the World Health Organization's (WHO) classification systems for invasive cervical cancer use the presence of

Figure 5. Immunohistochemical stain for cytokeratin (A) or carcinoembryonic antigen (B) (objective magnification ×40).
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Table 2. Clinical Characteristics of Patients With Clear Cell Adenosquamous Carcinoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>FIGO stage</th>
<th>Race</th>
<th>Therapy</th>
<th>Tumor size (cm)</th>
<th>Lymph nodal status</th>
<th>Time of recurrence</th>
<th>Length of follow-up</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>IB</td>
<td>White</td>
<td>RT</td>
<td>5.0</td>
<td>Negative</td>
<td>9 mos.</td>
<td>14 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>IB</td>
<td>White</td>
<td>OPE, RT CHT</td>
<td>3.0</td>
<td>Negative</td>
<td>22 mos.</td>
<td>22 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>IB</td>
<td>Hispanic</td>
<td>OPE, RT</td>
<td>8.0</td>
<td>Positive</td>
<td>9 mos.</td>
<td>30 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>IB</td>
<td>White</td>
<td>RT</td>
<td>NA</td>
<td>Negative</td>
<td>22 mos.</td>
<td>59 mos.</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>IB</td>
<td>White</td>
<td>OPE</td>
<td>5.0</td>
<td>Negative</td>
<td>30 mos.</td>
<td>51 mos.</td>
<td>NED</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>II A</td>
<td>African-American</td>
<td>RT</td>
<td>8.0</td>
<td>Negative</td>
<td>30 mos.</td>
<td>24 mos.</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>II B</td>
<td>White</td>
<td>OPE, RT</td>
<td>5.0</td>
<td>Positive</td>
<td>9 mos.</td>
<td>17 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>II B</td>
<td>African-American</td>
<td>RT, CHT</td>
<td>NA</td>
<td>Negative</td>
<td>10 mos.</td>
<td>16 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>II B</td>
<td>Hispanic</td>
<td>RT, CHT</td>
<td>6.0</td>
<td>Positive</td>
<td>8 mos.</td>
<td>8 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>II B</td>
<td>African-American</td>
<td>RT</td>
<td>NA</td>
<td>Negative</td>
<td>6 mos.</td>
<td>11 mos.</td>
<td>DOD</td>
</tr>
<tr>
<td>11</td>
<td>74</td>
<td>NA</td>
<td>Hispanic</td>
<td>RT</td>
<td>NA</td>
<td>Negative</td>
<td>3 mos.</td>
<td>4 mos.</td>
<td>AWD</td>
</tr>
</tbody>
</table>


glandular elements as a criteria for adenocarcinomatous differentiation. In addition, in seven (100%) of the seven cases for which paraffin blocks were available, mucin was identified using a mucicarmine stain. Although there is considerable controversy as to the classification of cervical cancers that produce mucin but lack architectural evidence of glandular differentiation, mucin production generally is considered to be evidence of adenocarcinomatous differentiation in carcinomas at most clinical sites.

The second reason for classifying these tumors as an adenosquamous carcinoma is that the solid sheets of vacuolated (e.g., glycogenated) cells characteristic of these tumors are similar to areas previously described in squamous cell carcinomas of the cervix. Occasional squamous cell carcinomas of the cervix contain sheets of cells with abundant cytoplasmic glycogen and have been referred to as squamous cell carcinomas with glycogenated cytoplasm. An additional factor suggesting that these cases represent a variant of adenosquamous carcinoma was the finding of foci of spindle-shaped cells with abundant eosinophilic cytoplasm suggesting squamous differentiation in two cases. It should be emphasized, however, that none of the current cases contained keratin pearls, individual cell keratinization, or prominent intercellular bridges, and that in the absence of clear-cut histologic squamous differentiation, we cannot unequivocally prove that these tumors represent adenosquamous carcinomas, rather than pure adenocarcinomas.

The differential diagnosis of clear cell adenosquamous carcinoma includes clear cell carcinoma and glassy cell carcinoma, both of which can have areas composed of masses of cells with abundant cytoplasm. However, clear cell carcinoma and glassy cell carcinoma have distinctive histologic or clinical features allowing them to be differentiated from clear cell adenosquamous carcinoma (Table 3). In addition to solid areas composed of cells with a vacuolated, glycogen-rich cytoplasm similar to those observed in clear cell adenosquamous carcinoma, clear cell carcinomas usually also have distinctive papillary and tubulocystic areas. Moreover, cells with an eosinophilic granular cytoplasm and hobnail cells with scant cytoplasm and prominent nuclei that project into the lumens of the tubulocystic areas are characteristic of clear cell carcinoma. Both of these types of cells are not found in clear cell adenosquamous carcinoma. Moreover, unlike clear cell adenosquamous carcinoma, clear cell carcinomas are not associated with HPV-18, but instead, are associated with a history of intrauterine diethylstilbestrol exposure in two-thirds of cases.

Although considered by some to be a rare variant of adenosquamous carcinoma, the most recent WHO classification of cervical cancers considers glassy cell carcinoma to be an entirely separate entity. Clear cell adenosquamous carcinoma and glassy cell carcinomas are composed of solid masses of cells with prominent cellular borders. However, unlike the cells in clear cell adenosquamous carcinoma, the cells in glassy cell carcinomas are not vacuolated; instead, they have an abundant amphophilic or pale eosinophilic cytoplasm that has a characteristic ground glass appearance. Moreover, the cells in glassy cell carcinomas are characterized by large, oval nuclei with finely granular chromatin and with prominent nucleoli. In contrast, the nuclei of clear cell adenosquamous carcinoma are smaller, more irregular, have a more granular chromatin distribution, and usually lack prominent nucleoli.
Table 3. Characteristic Features of Clear Cell Adenosquamous Carcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Clear cell adenosquamous carcinoma</th>
<th>Clear cell carcinoma</th>
<th>Glassy cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid areas</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Focal glandular formations</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Papillary or tubulocystic areas</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hobnail cells</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Vacuolated cytoplasm</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Eosinophilic or granular cytoplasm</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Focal mucin production</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Focal keratinization</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Large oval nuclei with prominent nucleoli</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Distinct cell borders</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Focal intracellular bridges</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Exclusively associated with HPV 18</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus.

One of the most striking features of clear cell adenosquamous carcinoma of the cervix was the exclusive association of these tumors with HPV-18; all 11 of the cases included in this series were associated with HPV-18. Although most recent large studies have detected HPV DNA in more than 80% of invasive squamous cell carcinomas, in most studies, HPV-16 is the predominant HPV type associated with invasive squamous cell carcinoma of the cervix. Human papillomavirus-18 is commonly found in association with other specific histologic types of invasive cervical cancer. One series of small cell undifferentiated carcinomas of the cervix detected HPV-18 in 14 (70%) of 20 cases. Similarly, HPV-18 is frequently associated with invasive adenocarcinomas and adenosquamous carcinomas of the cervix (Table 4). Using in situ hybridization, Tase et al. detected HPV-18 DNA in 8 (18%) of 44 adenosquamous carcinomas of the cervix. Using the polymerase chain reaction to identify HPV DNA, Yamakawa et al. detected HPV-18 DNA in 10 (48%) of 21 adenosquamous carcinomas of the cervix, and using Southern blot analysis, Walker et al. identified HPV-18 DNA in 3 (27%) of 11 adenosquamous carcinomas. However, in none of these series has the association between a specific type of HPV and a specific histologic type of invasive cervical cancer been as strong as the association between HPV-18 and clear cell adenosquamous carcinoma.

Clear cell adenosquamous carcinoma appears to be a relatively uncommon neoplasm. The 11 cases reported here were identified from among 157 tumors originally classified as invasive cervical adenocarcinomas. However, despite the fact that it is uncommon, we...
believe that it is important to recognize this entity because of its poor prognosis. The overall tumor recurrence rate in the 11 women included in this series was 73%, and there was a 64% death rate. Even among women with Stage IB tumors, survival was poor. Three (60%) of the five women with Stage IB clear cell adenocarcinoma died of their cervical disease. For comparison, the reported 5-year survival for women with Stage IB invasive cervical adenocarcinoma of all histologic subtypes is approximately 75%.39-41 Several years ago, it was suggested that cervical cancers associated with HPV-18 occurred in younger women, were more likely to be associated with lymph node involvement when classified as low stage, and had a worse prognosis than tumors associated with other types of HPV.34,42-45 Although other series have not confirmed an association between HPV type and clinical outcome,33,34,44,45 the clear cell adenosquamous carcinomas described in this report occurred in relatively young women (mean age, 43 years), had aggressive clinical courses, and were associated with HPV-18. However, before concluding that these tumors have a particularly aggressive clinical course, additional studies are required comparing outcome of clear cell adenosquamous carcinoma with cervical cancers of a similar size and stage, but of a different histologic type.

References