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Endometrial Endometrioid Adenocarcinoma of the Uterine Corpus Involving the Cervix: Some Cases Probably Represent Independent Primaries

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Summary

The majority of endometrial endometrioid adenocarcinomas involving the cervix have tumor morphology that is similar in the endometrium and the endocervix. There are, however, some cases in which the morphology of the tumor in the endocervix is different from the endometrial carcinoma, in which it is more invasive than the endometrial carcinoma, or in which invasion only occurs in the endocervix while there is no or only minimal myometrial invasion. The goal of this study was to investigate whether tumors involving the endometrium and the endocervix are similar or 2 independent primaries by hematoxylin and eosin stain, immunohistochemistry (IHC), human papillomavirus (HPV) DNA *in situ* hybridization, RNA reverse transcriptase *in situ* polymerase chain reaction (PCR) analyses to reveal HPV, and DNA clonality studies. We selected 14 cases of endometrial endometrioid adenocarcinomas involving the cervix with complete pathology material available from the years between 1968 and 2004. Immunohistochemical studies for vimentin, carcinoembryonic antigen, estrogen receptor, progesterone receptor, and p16 were performed in 12 cases; HPV DNA/RNA analyses in 4 cases; and clonality studies in 9 cases. The patients' ages

ranged from 42 to 81 years (mean: 62 y). Follow-up information was obtained in 11 patients. Histologic features varied between the tumors in the endometrium and the endocervix in 8 cases, and 5 of these cases had uniform, dilated glands having a microcystic appearance in the cervix. In 6 cases, the tumors in the endometrium and the endocervix had similar histologic features. The immunohistochemical studies showed some differences between the endometrial and endocervical adenocarcinomas in 8 of the 12 cases, independent of differing or similar histologic features. HPV testing in 4 of the cases (3 with similar and 1 with different histology) yielded similar results in the endometrium and endocervix: 2 cases were negative, 1 was positive and 1 was equivocal for HPV DNA/RNA analyses. Clonality studies showed differences between the adenocarcinoma in the endometrium and the endocervix in 7 cases, including 5 cases with different histologic appearances; 2 cases had similar loss of heterozygosity patterns. In conclusion, as suggested by clonality studies, coexisting endometrial and endocervical carcinomas with different histologic features are most likely independent neoplasms. Endometrial and endocervical carcinomas that have similar appearances can represent either the same neoplasm or independent primaries. Clonality tests may help determine their relationship. IHC studies may not be helpful for synchronous endometrial and endocervical tumors, especially those of endometrioid type. It is possible that IHC identifies cell differentiation, rather than site of origin. HPV studies are important to identify endocervical tumors associated with high-risk HPV. However, endometrial tumors involving the cervix and endocervical tumors unrelated to HPV are both negative for high-risk HPV.

Keywords

Endometrial adenocarcinoma; Endocervical adenocarcinoma; Endometrioid type; Microcystic pattern

The majority of endometrial endometrioid adenocarcinomas (EEA) that involve the cervix have similar histologic features in the endometrium and the endocervix. This feature indicates progression of the endometrial tumor from the uterine body to the cervix (1–3). However, we have observed some cases in which the tumor involving the endocervix is histologically different from the endometrial carcinoma, or in which invasion occurs in the endocervix and there is no or only minimal myometrial invasion. These carcinomas have endometrioid features and are therefore different from the classical endocervical adenocarcinoma, which has mucinous differentiation.

Cervical involvement by endometrial malignancies has long been known to be an adverse prognostic factor (3–5). However, the prognostic value of the subdivision of stage II (Iia, endocervical gland involvement and Iib, endocervical stromal involvement) has been questioned by some studies, and some studies have found that the outcome of stage IIa tumors is significantly better than that of stage Ic tumors (6–8). In addition, the concept of stage IIa endometrial adenocarcinoma is problematic, because in the absence of an endometrial adenocarcinoma the endocervical neoplasm would be diagnosed as a primary endocervical adenocarcinoma *in situ*.

The goal of this study was to investigate by hematoxylin and eosin (H&E) stain, immunohistochemistry, human papillomavirus (HPV) DNA *in situ* hybridization, HPV RNA

reverse transcriptase (RT) *in situ* polymerase chain reaction (PCR) analyses, and DNA clonality studies whether tumors synchronously involving the endometrium and the endocervix represent 1 neoplasm or 2 independent primaries.

MATERIALS AND METHODS

We reviewed the pathology reports of 577 patients at MD Anderson Cancer Center who were diagnosed with endometrial carcinoma between 1968 and 2004. From this group, we selected 14 cases of EEA that involved the cervix during the 37-year period. These cases were selected on the basis of the following criteria: the histology of the endometrial adenocarcinoma was pure endometrioid; the adenocarcinoma also involved the cervix, either glands or stroma, but without continuity from the endometrial adenocarcinoma; microscopic slides were available for review; and paraffin blocks or unstained slides from the endometrium and the endocervix were available to perform additional studies. Clinical information including age, race, medical and family history, parity, gravidity, hormone exposure, surgical stage of disease, treatment, and outcome was obtained by retrospective chart review. Five to sixty (average 17) H&E-stained slides were examined to confirm the diagnosis. There were 3 to 10 (average 6) slides from the endometrium and 1 to 6 (average 2) slides from the cervix. The histopathologic materials were reviewed by 2 of the authors (L.J. and E.G.S.).

The histopathologic material reviewed included all diagnostic biopsy or curettage specimens, the hysterectomy and salpingo-oophorectomy specimens and any additional material resected at the same time (lymph node samples and omental specimens), and samples from any recurrence or metastasis excised afterward. The histopathologic data recorded were as follows: (1) histologic features and International Federation of Gynecology and Obstetrics (FIGO) grade of the tumor in the endometrium and the endocervix, (2) size and location of the tumor in the hysterectomy specimen, (3) presence or absence of squamous metaplasia, (4) presence or absence of myometrial invasion with evaluation of the depth of invasion, (5) presence or absence of endocervical stromal invasion with evaluation of the depth of invasion, and (6) presence or absence of tumor invasion in the lymphatic or vascular spaces within the myometrium and cervix.

Paraffin blocks or unstained slides were required to perform immunohistochemistry, *in situ* hybridization for HPV DNA, *in situ* PCR for viral RNA, and clonality studies. However, if the available material was scanty, we performed only 1 or 2 of these tests.

In 12 cases, immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue sections of the endometrium and the endocervix, using the avidin-biotin-peroxidase complex method (LSAB2 kit; DAKO, Carpinteria, CA) with heat-induced antigen retrieval. The antigen-antibody reaction was visualized using 3-amino-9-ethylcarbazole or diaminobenzidine. The monoclonal antibodies were directed against vimentin (Ventana, Tucson, AZ), carcinoembryonic antigen (CEA) (Labvision, Fremont, CA), estrogen receptor (ER) (Novocastra, Hingham, MA), progesterone receptor (Labvision), and p16 (Labvision).

Four cases were chosen on which to perform HPV DNA *in situ* hybridization and HPV RNA RT *in situ* PCR analyses. *In situ* hybridization was carried out using the Benchmark HPV *in situ* hybridization system of Ventana Medical Systems (Tucson, AZ). In brief, multiple 4- μ m sections were placed on sequentially labeled silane-coated slides. The tissue was deparaffinized, proteased, and washed, and then co-denatured with a probe cocktail containing labeled probes that can detect HPVs 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68, and 70. The HPV probetarget complex was observed due to the action of alkaline phosphatase on the chromogen nitroblue tetrazolium and bromochloroindolyl phosphate. Nuclear fast red served as the counterstain.

The protocol of RT *in situ* PCR has been described earlier (9). Optimal protease digestion time was first determined using nonspecific incorporation of the reporter nucleotidedigoxigenin dUTP as a guide. Optimal protease digestion was followed by overnight incubation in Rnase free-Dnase (10 μ L per sample, Boehringer Mannheim, Indianapolis, IN) and one-step RT/PCR using the rTth system and digoxigenin dUTP. Analyses were carried out for HPV 16, HPV 18, and HPV 11 RNA, as well as consensus HPV RNA, which can detect most genital HPV types. The primer sequences for HPV 16 and HPV 18 RNA correspond to the open reading frames E6 and E7, and have been published earlier (9). After 25 cycles, the digoxigenin-labeled cDNA was detected due to the action of alkaline phosphatase on the chromogen nitroblue tetrazolium and bromochloroindolyl phosphate. Nuclear fast red served as the counterstain. Biopsy material from histologically normal cervixes (5 cases) removed for leiomyoma served as the negative controls for both the DNA and RNA analyses.

Nine cases were chosen with which to conduct the tumor clonality study. Five-micron thick sections were obtained and stained with H&E. Microdissection was performed under light microscopy visualization using a 30-gauge needle. Adjacent cells from normal tissue were microdissected and used as a normal control. Microdissected tissue was suspended in a lysis buffer containing 0.5 mg/mL proteinase K, 0.5% Tween-20, 1 mM ethylenediaminetetraacetic acid pH 8.0, and 50 mM Tris-HCl (pH 8.5), and was incubated at 56°C for 48 hours with 2 additional doses of proteinase K. Samples were then heated to 95°C for 5 minutes to inactivate the proteinase K. To aid in purification, 10 μ g of yeast tRNA was added to each DNA sample. To purify the DNA, samples were extracted with an equal volume of phenol, followed by extraction with an equal volume of chloroform. They were then precipitated with Pellet Paint NF Co-Precipitant P (Novagen, Gibbstown, NJ) according to the manufacturer's directions, and the pellets were resuspended in 25 μ L H₂O. About 1 μ L of DNA was used in PCR with primers for microsatellite markers D1S201, D3S1300, D6S250, D10S215, D10S541, D17S791, D17S796, D18S483, IL2RB, TP53, and ER according to established protocols. PCR primer sequences were obtained from the GDB Human Genome Database and primers were custom-synthesized by Applied Biosystems (Gibbstown, NJ). PCR products were diluted ten-fold into formamide, and 2 μ L of this dilution was added to 12 μ L of a dilution of ROX 500 marker. The samples were denatured at 95°C for 5 minutes, transferred to ABI 310 sample tubes, and loaded on the ABI 310 genetic analyzer.

RESULTS

Clinical information for the fourteen cases is summarized in Table 1. The patients ranged in age from 42 to 81 years (mean: 62 y). Follow-up information was obtained in eleven patients. The mean follow-up time was 33 months (range: 3 to 88 mo). Twelve patients were treated by total abdominal hysterectomy/bilateral salpingo-oophorectomy and 1 patient by VH/bilateral salpingo-oophorectomy. One patient's treatment included only endometrial biopsy and cervical conization. All patients except one had adjuvant radiation therapy and/or chemotherapy.

The FIGO surgical stages of the 13 cases with surgical treatment were as follows: 1 stage IIa; 9 stage IIb, including 1 case with a synchronous ovarian tumor; and 3 stage III with pelvic lymph node metastases. Of 13 surgical specimens, 1 (case 7) had no myometrial invasion, 8 had less than 50% invasion (cases 1, 3, 4, 6, 9, 10, 12, and 13), and 4 had more than 50% invasion (cases 2, 5, 8, and 11). Lymphovascular invasion was present in 5 cases. The FIGO grades of the 14 cases were as follows: 3 grade 1, 10 grade 2, and 1 grade 3.

Histologic features differed between the tumors involving the endometrium and the endocervix in 8 cases (Figs. 1, 2). The pathologic characteristics of these tumors are summarized in Table 2 (cases 1 to 8). In 5 of the cases the adenocarcinoma had a microcystic pattern involving the cervix, characterized by a diffuse pattern of infiltrating glands. The glands have a bland appearance and are formed by low cuboidal and flat epithelial cells without significant atypia. Mitotic figures are rare and necrosis is usually absent. The flat cells lining the dilated glands produce a microcystic pattern, which is recognized as malignant because of diffuse infiltration. Adenocarcinoma *in situ* is not present in these cases.

Six cases had similar histologic features, including the same FIGO grades, in the endometrial and the endocervical tumors; these features are summarized in Table 3 (cases 9 to 14).

The results of the additional studies, including immunohistochemical stains, HPV DNA/RNA *in situ* analyses, and clonality, are summarized in Table 4.

Immunohistochemical studies were performed in 12 cases. In 8 of these cases there were differences in the staining pattern between endometrium and endocervix by 1 marker in 5 cases and by 2 markers in 3 cases. In the only case in which the staining pattern was similar in the endometrium and the endocervix (case 13), it was consistent with an endocervical primary. Figures 3A, B, and C show the results of the immunohistochemical stains in case 10.

As is evident in Table 4, there was sufficient tissue for HPV testing in 4 of the cases. In each case, the tumors in the endometrium and the endocervix had similar results by HPV DNA by *in situ* hybridization, which has a detection threshold of 10 copies per cell. These results were confirmed by HPV RNA using RT *in situ* PCR, which can detect 1 HPV genome per cell. Two cases (3 and 14) were negative for HPV, 1 case (10) was positive for HPV 18, and

1 case (11) was negative for high-risk HPV DNA by *in situ* hybridization. This case was positive for HPV 11.

The DNA obtained was of poor quality in 1 of 10 cases (case 11), and therefore this case was not included in the loss of heterozygosity (LOH) study. Five of the cases with differing histology had dissimilar patterns of LOH, with 4, 3, 2, and 1 (2 cases) markers suggestive of 2 independent primaries. Of the 4 cases with similar histology, 2 had the same patterns of LOH, whereas the other 2 cases had different patterns of LOH with 2 markers.

DISCUSSION

The involvement of both the endometrium and endocervix by endometrioid adenocarcinoma is usually considered to reflect an endometrial primary extending into the cervix. This feature defines cases of stage II endometrial adenocarcinoma, which are subclassified as IIa when only the endocervical epithelium is involved and IIb when the carcinoma also involves the stroma of the cervix. The concept of stage IIa is problematic because intraepithelial metastases are rare, and in the absence of an endometrial carcinoma, the cervical lesion would be considered an endocervical adenocarcinoma *in situ*. However, this type of adenocarcinoma is endometrioid, different from the conventional endocervical adenocarcinoma *in situ*. Other features that raise questions about the classification of stage II endometrial carcinoma is the presence in some cases of endocervical involvement in the absence of myometrial invasion, the presence of a larger mass in the endocervix than in the endometrium, and the presence of a carcinoma in the cervix with some histologic features different from the endometrial carcinoma involving the endometrium. In addition, stage II adenocarcinoma of the endometrium always involves mainly the endocervix; there are no cases involving only the exocervix. Other authors have recently questioned the significance, validity, and reproducibility of stage II endometrial cancer and FIGO-eliminated cases with involvement of the endocervical epithelium as stage IIA cases (11–13).

We initiated this study because we noted that in some cases the neoplasms in the endometrium and endocervix had very different histologic appearances. In this study, the first 8 cases we reviewed had different histologic appearances, including a peculiar microcystic pattern in the endocervix in cases 1, 3, 4, 6, and 7; squamoid changes only in the endocervix in case 2; and a different grade of tumor involving the endocervix in cases 5 and 8. The only clinical difference that we found between these 8 cases and the 6 cases that had similar histologies in the endometrium and endocervix was that 3 of the 8 patients (37.5%) with differing histologies had received hormonal therapy, whereas only 1 of the 6 patients (16.6%) with similar histologies had received hormonal therapy.

Following the logic of the current staging system for endometrial carcinoma, one would expect that only patients with significant myometrial invasion would have involvement of the cervix and that the tumor in the cervix should have similar histologic features and a similar or higher FIGO grade compared with that in the endometrium. However, this was not true in seven of the 14 cases. In case 7, the endometrial tumor did not invade the myometrium, but the endocervical neoplasm deeply invaded the cervical stroma. In cases 1, 3, 4, 6, and 13, the endometrial tumor only superficially invaded the myometrium, but the

endocervical tumor deeply invaded into the endocervix (over 50% of the endocervical wall). In cases 1, 3, 4, 6, and 7 the histologic appearance of the tumor in the cervix was different from that of the endometrial carcinoma.

With regard to the results of immunohistochemical studies, it is interesting that of the 12 cases evaluated, there was only 1 (case 13) in which all of the markers favored an endocervical carcinoma. Of the other 11 cases, immunohistochemistry showed discordant results between the tumor in the endometrium and that in the endocervix in 8 cases. Although, the overall results favor an endometrial origin, the main marker showing differences between the tumors at both sites was p16. In 5 cases, there was a difference in the percentage of positive cells stained. Vimentin showed a difference between both tumors in 3 cases, CEA in 2, and progesterone receptor in one. Of the 8 cases showing differences in the staining of the tumor at both locations, clonality studies were conducted in 6, and in 5 of these cases there was a clear difference between the tumors at both locations.

High-risk HPV DNA *in situ* hybridization and RNA *in situ* PCR were performed in 4 cases; 1 case (case 3) had different histologic features and 3 cases (cases 11, 13, and 14) had similar histologic features in the endometrium and cervix. All 4 tumors in the endocervix and endometrium had similar results. Cases 3 and 4 were negative, case 13 was positive, and case 11 was equivocal by HPV *in situ* hybridization but negative by PCR.

The results of the clonality study in 9 cases showed differences between the adenocarcinomas in the endometrium and the endocervix in 7 cases, which included all 5 cases tested (100%) that had different histologic appearances, cases 1 to 5, and 2 cases that had similar histologies in the endometrium and endocervix (cases 12 and 14).

In our opinion, when the histologic appearance of the neoplasms in the endometrium and endocervix is different and both neoplasms also have different results in clonality studies, they represent independent primaries (cases 1, 2, 3, 4, and 5). When the histology of both neoplasms is similar but they show differences in clonality studies, they could represent independent primaries or they may have different clonality due to genetic progression (cases 12 and 14). When the histology is similar, and additional tests on both neoplasms show the same results, they are from one primary. In case 13, the primary tumor is most likely endocervical on the basis of the immunohistochemical staining patterns, the positive HPV DNA/RNA analysis in the endocervical and endometrial tumor, and the LOH of D10S215 in both neoplasms.

The endocervical tumors in these cases are histologically endometrioid, and this is probably the reason for the confusing immunohistochemical results. Several studies have shown differences in the immunohistochemical staining pattern of endocervical and endometrial adenocarcinomas (10,14,15); however, in most endocervical adenocarcinomas there is mucinous differentiation, which is reflected in the results of the immunohistochemistry (eg, CEA). As all of the cases in this study were endometrioid carcinomas, and most primary endocervical carcinomas not associated with endometrioid carcinomas have some mucinous component, it is possible that immunohistochemistry in this situation may identify tumor differentiation rather than site of origin. Alternatively, it is possible that endocervical

adenocarcinomas associated with endometrial carcinomas are a different type of endocervical neoplasm. It is believed that EEA is hormone-related, whereas endocervical adenocarcinoma is associated with high-risk HPV infection (16,17). These features have been used to differentiate endometrial versus endocervical tumors, and primary versus metastasis, through immunohistochemical studies and HPV DNA analysis. Usually, the results of the different studies are in agreement. However, some of the cases in this study had similar immunohistochemical staining patterns and HPV analysis results for the tumors in the endometrium and the endocervix, whereas the clonality results were different. It is possible that endocervical adenocarcinomas associated with endometrial adenocarcinomas are of endometrioid type, and therefore the immunohistochemical staining pattern of these neoplasms is similar to that of the endometrial endometrioid tumors. These neoplasms may be hormone-related and unrelated to HPV.

Adenocarcinomas with a pattern similar to some of the tumors presented here involving the cervix have been described in the literature as an unusual type of endometrial carcinoma extending into the cervix with a burrowing pattern (18). In the cases with this pattern in this study, there were not only significant differences in the histologic features between the endometrial adenocarcinoma and the endocervical neoplasm, but also in the clonality. These differences suggest that they may represent 2 independent primaries, rather than endocervical involvement by endometrial adenocarcinoma.

On the basis of the results of our study, we propose the following:

1. When coexisting endometrial and endocervical carcinomas have different histologic features, they are most likely independent neoplasms. In this study, 5 cases with different histologic appearances had different clonality results. Therefore, we believe that the endometrial and endocervical tumors were independent neoplasms in these 5 cases.
2. When the endometrial and endocervical carcinomas have a similar appearance, they may represent either the same neoplasm or independent primaries. If necessary, clonality tests could be performed.
3. Immunohistochemical analysis may not be helpful when a patient has coexisting endometrial and endocervical tumors, especially endometrioid type. Immunohistochemistry might identify tumor differentiation rather than site of origin.
4. Although HPV studies identify most endocervical adenocarcinomas, not all adenocarcinomas of the endocervix are HPV-related. Therefore, a negative HPV test, by *in situ* hybridization or PCR, does not rule out a primary endocervical adenocarcinoma.

On the basis of our findings, we believe that some coexisting endocervical and endometrial adenocarcinomas represent independent primaries. This would explain why patients with stage II disease were shown to have a better prognosis than patients with stage Ic disease in some studies (7,8). Moreover, we believe that before concluding that a patient has stage II endometrial cancer, it is necessary to conduct additional studies on the endometrial and

endocervical neoplasms, especially those with histologic differences. Clonality studies may help to determine whether the cervical neoplasm is indeed an extension of the endometrial tumor, or a new primary endocervical adenocarcinoma.

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FIG. 1.

(A) (case 3), Endometrioid adenocarcinoma involving the endometrium. (B) (case 3), In the cervix the carcinoma has an infiltrating pattern with uniform, dilated glands having a microcystic appearance.

FIG. 2.

(A) (case 4), Endometrioid adenocarcinoma in the endometrium. (B) (case 4), A carcinoma with different histologic appearance in the cervix having a microcystic pattern.

FIG. 3.

(A) (case 10), Endometrioid adenocarcinoma focally positive for p16. (B) (case 10), Endometrioid adenocarcinoma in the endometrium diffusely positive for estrogen receptor. C (case 10), Endometrioid adenocarcinoma in the endocervix diffusely positive for estrogen receptor.

TABLE 1.

Clinical information for 14 patients

Patient	Age (yr), race	Medical and family history	Hormone exposure	Parity and gravidity	Surgical stage of disease (FIGO)	Treatment	Follow-up (mo) and outcome
1	67, W	History of depression	None	G2P2	IIb	TAH, BSO, and radiotherapy	77, NED
2	42, W	History of smoking 48 pack-years; hypertension	4 mo	G3P3	IIb	TAH, BSO, and radiotherapy	88, NED
3	81, W	Hypertension and coronary artery disease; 2 sisters with breast cancer	Unopposed estrogen therapy for 10 yr	G0P0	IIb	TAH, BSO (no other therapy due to significant medical history)	42, died of other disease
4	80, W	N/A	N/A	G4P4	III	TAH, BSO, and radiotherapy	24, NED
5	48, H	None	None	G0P0	III	TAH, BSO, radiotherapy, and chemotherapy	3, NED
6	78, W	N/A	N/A	N/A	IIb	TAH, BSO, and radiotherapy	24, died of the disease
7	60, W	None	Hormone replacement for 6 yr	G2P2	IIb	LAVH, BSO, and radiotherapy	28, NED
8	46, B	Significant family history of colon cancer and breast cancer	None	N/A	IIb	TAH, BSO, radiotherapy, and chemotherapy	N/A
9	68, B	Hypertension, schizoaffective disorder	N/A	G0P0	IIa	TAH and BSO	N/A
10	51, W	BCC on neck and face	OCP for 10 yr	G1P1	IIb (synchronous right ovarian tumor)	TAH, BSO, and radiotherapy	21, NED
11	73, W	None	None	G3P3	III	TAH, BSO, and radiotherapy	22, died of the disease
12	42, H	N/A	N/A	G0P0	IIb	TAH and left salpingo-oophorectomy	18, NED
13	48, W	N/A	N/A	G0P0	IIb	TAH and BSO	N/A
14	76, W	N/A	N/A	N/A	Endometrial biopsy and cervical conization specimen only	N/A	17 NED

A indicates Asian; B, Black; BSO, bilateral salpingo-oophorectomy; H, Hispanic; LAVH, laparoscopic assisted vaginal hysterectomy; N/A, not available; NED, no evidence of disease; TAH, total abdominal hysterectomy; W, White.

TABLE 2.
Summary of 8 cases with different histologic features in the endometrial and endocervical tumors

Patient no.	FIGO stage	FIGO grade	Size and location of tumor in the endometrium	Myometrial invasion/full thickness of uterine wall (mm)	Size/location of tumor in the endocervix	Endocervical stromal invasion/full thickness of cervical wall (mm)	Histologic features—all endometrioid except	Studies performed
1	IIb	2	30 mm nodule at the fundus	4/14.5	15 mm nodule at cervical canal	15/16	Microcystic pattern in the endocervix	Immunohistochemistry, HPV DNA/RNA <i>in situ</i> analyses, and clonality
2	IIb	2	45 mm mass involving entire cavity	11–12/23	Upper half of the endocervix	Mucosa and stroma (no full thickness of cervical wall available)	More squamoid change in the endocervix	Clonality
3	IIb	1	Diffusely thickened endometrium, up to 5 mm	2/18	Upper half of the endocervix	9/11	Microcystic pattern in the endocervix	Immunohistochemistry, HPV DNA/RNA <i>in situ</i> analyses, and clonality
4	III	2	Diffusely thickened and necrotic endometrium, up to 3 mm	3.2/32	4-mm endocervical polypoid mass	Full thickness of cervix	Microcystic pattern in the endocervix	Immunohistochemistry and clonality
5	III	2	Diffusely thickened endometrium, up to 25 mm	20/25	Entire endocervical canal	17/25	FIGO grade I at endometrium; FIGO grade II in the endocervix	Immunohistochemistry, HPV DNA/RNA <i>in situ</i> analyses, and clonality
6	IIb	1	N/A	3/14	N/A	6/8	Microcystic pattern in the endocervix	Immunohistochemistry
7	IIb	2	N/A	No myometrial invasion	N/A	5/7	Microcystic pattern in the endocervix	Immunohistochemistry
8	IIb	3	60 mm at the fundus and upper portion of the cavity	26/28	No tumor identified on gross exam	Small focus (1 mm) in the upper endocervical stroma	FIGO grade III and undifferentiated carcinoma in the endometrium; FIGO grade II with clear cell change in the endocervix	Immunohistochemistry

HPV indicates human papillomavirus; N/A, not available.

TABLE 3.
Summary of 6 cases with similar histologic features in the endometrial and endocervical tumors

Patient no.	FIGO stage	FIGO grade	Size and location of tumor in the endometrium	Myometrial invasion/full thickness of uterine wall (mm)	Size/location of tumor in the endocervix	Endocervical stromal invasion/full thickness of cervical wall (mm)	Histologic features	Studies performed
9	IIa	2	Diffusely thickened endometrium of 17 mm	12/28	No tumor identified on gross exam	N/A	Endometrioid	Clonality
10	IIb (synchronous right ovarian tumor)	2	5 × 5 mm posterior lower uterine segment	1/18	Extending to upper endocervix	1-mm deep (no full thickness of cervical wall)	Endometrioid with papillary features	Immunohistochemistry
11	III	2	Necrotic endometrium	> 50%	Extending to the entire cervix	Involving both mucosa and stroma	Endometrioid	Immunohistochemistry, HPV DNA/RNA analyses, and clonality
12	IIb	2	20-mm lower uterine segment	2/17	Grossly no tumor present in the cone biopsy specimen or hysterectomy specimen	3.2 mm deep in the cone biopsy specimen	Endometrioid with extensive papillary areas	Immunohistochemistry and clonality
13	IIb	2	40-mm cystic structure and 15-mm solid area, 1 cm apart, in the lower uterine segment	2/20	No tumor identified on gross exam	14/20	Endometrioid	Immunohistochemistry, HPV DNA/RNA <i>in situ</i> analyses, and clonality
14*	IIb	1	N/A	N/A	N/A	30/30	Endometrioid	Immunohistochemistry, HPV DNA/RNA analyses, and clonality

* Endometrial biopsy and cervical biopsy specimen only.

HPV indicates human papillomavirus; N/A indicates not available.

TABLE 4.

Summary of the immunohistochemical studies, HPV DNA probe, and clonality tests performed on 12, 4, and 9 cases (Fig. 5) (cases 1 to 8 with different histologic features; cases 9 to 14 with similar histologic features)

Patient no.	Vimentin		CEA		ER		PR		p16		ISH and PCR DNA/RNA <i>in situ</i> analyses for high-risk HPV				Clonality	
	EnM	EnCX	EnM	EnCX	EnM	EnCX	EnM	EnCX	EnM	EnCX	EnM	EnCX	EnM	EnCX	EnM	EnCX
1	+	+	-	-	+	+	+	+	60% +	10% +	N/A	N/A	LOH of DIS201 D10D215 w/MSI	N/A	LOH of D10S215	
2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	LOH of D3S1300, IL2RB, TP53, D6S250	N/A	LOH of ER, borderline of D10S541	
3	+	-	-	-	+	+	+	+	80% +	30% +	-	-	LOH of DIS201, TP53, D17D791, D17S796, ER; MSI in D10S541	-	LOH of D3S1300, D18S483, D17S791, ER; MSI of D10S215, TP53, D6S250	
4	+	+	+	-	+	+	+	+	50% +	80% +	N/A	N/A	No LOH	N/A	LOH borderline of D18S483, TP53	
5	+	+	-	-	+	+	+	+	5% +	20% +	N/A	N/A	LOH of ER	N/A	LOH of D10S541	
6	+	+	-	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7	+	+	-	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	+	+	-	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	LOH of D10S215	N/A	LOH of D10S215	
10	+	+	-	-	+	+	+	+	10% +	50% +	N/A	N/A	N/A	N/A	N/A	
11	Focal +	-	-	-	Focal +	+	+	+	40% +	40% +	ISH equivocal, PCR -	ISH equivocal, PCR -	N/A	N/A	N/A	
12	-	Focal +	-	Focal +	+	+	-	-	100% +	100% +	N/A	N/A	LOH of IL2RBD6S250	N/A	No LOH	
13	-	-	+	+	-	-	-	-	100%-	100% +	+	+	LOH of D10S215	+	LOH of D10S215	
14	+	+	-	-	+	+	-	+	30% +	30% +	-	-	No LOH	-	LOH of TP53, D10S541	

CEA indicates carcinoembryonic antigen; ER, estrogen receptor; EnCX indicates endocervix; EnM, endometrium; HPV, human papillomavirus; LOH, loss of heterozygosity; N/A, not available; PCR, polymerase chain reaction; PR, progesterone receptor.