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Original Article

Secondary Involvement of the Adnexa and Uterine Corpus by Carcinomas of the Uterine Cervix: A Detailed Morphologic Description

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Summary: Cervical carcinoma infrequently involves the uterine corpus or adnexa. Metastatic adenocarcinoma (AC) to the ovaries can be difficult to distinguish from primary ovarian tumors, and metastatic squamous cell carcinoma (SCC) to these sites has not been well described. Our aim was to provide a detailed description of the morphologic patterns of adnexal and corpus involvement by cervical carcinoma. Cases were identified over a 15-yr period and the following features were recorded: visible lesion, depth of invasion, lymphovascular invasion, and patterns of spread. Only usual human papillomavirus-associated tumors were included. Twenty cases with available slides were identified (2 *in situ* and 8 invasive SCC; 10 AC); 17 had visible lesions, usually with deep cervical and lymphovascular invasion. Sixteen involved the corpus (1 *in situ*, 7 SCC, 8 AC), all colonizing endometrium and 10 invading myometrium. SCC involved the ovary and fallopian tube in 4 and 6 cases, respectively, whereas AC involved the ovary in 4 (2 unilateral, 2 bilateral) and the tube in 8 cases. SCC in the ovary usually showed parenchymal invasion, and parenchymal and mucosal involvement in the tube. AC in the ovary ranged from small nodules to confluent expansile growth, whereas in the tube it often showed mucosal colonization mimicking a primary tubal process. Adnexal metastasis of cervical carcinoma is rare and usually coexists with endometrial and myometrial extension from the cervix. Both squamous and ACs can colonize tubal and endometrial mucosa; AC in particular can mimic primaries at those sites. Bilaterality is not a common feature of metastatic endocervical AC. **Key Words:** Cervix—Carcinoma—Metastasis—Corpus—Adnexa.

Carcinomas of the uterine cervix affect 500,000 women worldwide, half of whom will die of the disease every year (CDC fact sheet). Squamous cell carcinoma (SCC) is the most common histologic subtype and adenocarcinoma (AC) comprises approximately 25% of cases (1). The incidence of ovarian metastases ranges from 2% to 28.6% for cervical AC and 0% to 17.4% for SCC, depending on the stage of disease (2–6). The histologic appearance of cervical AC involving the ovaries has been well described, highlighting the propensity for these metastases to simulate primary ovarian surface epithelial neoplasms including borderline tumors and well-differentiated carcinomas (7,8). The pattern of ovarian involvement by cervical SCC is not well described, nor is the involvement of the uterine corpus and fallopian tubes by cervical carcinomas. In this study, we performed a detailed morphologic

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analysis of endocervical AC and cervical SCC with secondary involvement of adnexa (ovaries, fallopian tubes) and/or uterine corpus.

MATERIALS AND METHODS

The institutional database at Memorial Sloan Kettering Cancer Center was searched for patients diagnosed with cervical cancer with secondary involvement of the adnexa and/or uterine corpus between 1997 and 2012. SCC and human papillomavirus (HPV)-associated usual cervical ACs were included; other histologic variants such as clear cell, mesonephric, and gastric type were excluded. Pathologic reports and all available slides of the primary tumors and the secondarily involved sites were reviewed. The following clinicopathologic features were recorded: clinically visible tumor in cervix, tumor size, presence of lymphovascular invasion (LVI), and corpus and/or adnexal involvement. The following histologic patterns of involvement at each site were also recorded: colonization of preexisting epithelium, nodular versus infiltrating, laterality, presence of surface nodules, and ovarian size. The following features of ovarian involvement by AC were noted: papillary/villoglandular growth with or without glandular confluence and destructive stromal invasion. Expansile growth was defined as the presence of confluent glandular epithelium with cribriform areas but no desmoplastic stromal invasion. Destructive stromal invasion was categorized as invasive.

RESULTS

Clinicopathologic features of the cases are summarized in Table 1. Of 538 patients with cervical carcinoma who underwent surgery, there was secondary involvement of the adnexa and/or corpus in 20 patients meeting our criteria. The patients ranged in age from 32 to 73 yr (median = 45 yr), and the cervical carcinomas were invasive and *in situ*/high-grade squamous intraepithelial lesion (HSIL/CIN3) in 18 (90%) and 2 (10%) patients, respectively. The majority of patients with invasive carcinoma (17/18, 94%) presented with clinically visible lesions and advanced stage disease with metastases to the peritoneum (3/18) or lymph nodes (3/18).

The number of slides reviewed in each case ranged from 7 to 39 with a mean of 22. The histologic subtypes of the cervical tumors were: SCC (n = 8); AC (n = 9); HSIL/CIN3 with no invasive carcinoma (n = 2); and adenosquamous carcinoma (n = 1). The adenosquamous carcinoma (Patient 13) was composed mostly of glands with a minor squamous component and was therefore grouped with the ACs for the purposes of this study. One patient with AC (Patient 16) was found to have suspicious adnexal masses and positive lymph nodes on imaging. Bilateral adnexa and lymph nodes were removed for diagnostic purposes and no hysterectomy was performed due to advanced stage disease.

One patient (Patient 1) with cervical HSIL/CIN3 but no invasive carcinoma on cone biopsy showed diffusely metastatic SCC including extensive involvement of the ovary. She was human immunodeficiency virus (HIV)-positive and was found to have a focus in the cervix with an exuberant lymphocytic reaction in the stroma suggestive of regressed invasive carcinoma. The second patient with HSIL/CIN3 was undergoing a trachelectomy due to repeated positive margins on multiple cone biopsies (Patient 2). The trachelectomy was converted to hysterectomy without salpingo-oophorectomy for positive endocervical margin and tumor in the endometrial curettage at the time of surgery.

Of the 8 invasive SCC of the cervix, 7 involved the uterine corpus (1 case did not have a hysterectomy and therefore corpus involvement could not be evaluated). One of the HSIL cases involved the ovary and fallopian tube but not the corpus, whereas the other HSIL involved the endometrium only (adnexa not removed and therefore not evaluated). Four of the 7 SCC with corpus involvement also had adnexal involvement (2 tube only, 2 tubes and ovaries), whereas the other 3 showed no adnexal metastases. One case with metastatic SCC in bilateral ovaries and left fallopian tube did not have hysterectomy due to high-stage disease at time of surgery; therefore, the corpus was not assessed (Patient 6).

Of the 10 invasive ACs, 8 involved the uterine corpus (1 case did not have a hysterectomy and therefore corpus involvement could not be evaluated). Six of the 8 cases with corpus involvement also had adnexal involvement (3 tube only, 3 tubes and ovaries), whereas the other 2 showed no adnexal metastases.

LVI was identified in 7/8 invasive SCC and 6/10 AC. Two cases involved the adnexa only (1 HSIL, 1 AC), 6 the corpus only (1 HSIL, 3 SCC, 2 AC), and 10 involved both sites (4 SCC, 6 AC). When present in the fallopian tube, tumor was almost always present in the ovary or endometrium. Only 1 case (AC) had involvement of the fallopian tube without involvement of ovary or corpus (Patient 20).

TABLE 1. *Clinicopathologic features of cervical carcinomas with ovarian, fallopian tube and/or endometrial involvement*

					Corpus involvement		Ovarian involvement				FT involvement	
Patient	Age (yr)	Tumor type	Stage at diagnosis	LVI		Microscopic	Laterality	Ovary size (cm)	Gross	Microscopic	Laterality	Microscopic
1	37	HSIL*	IVB*	0	0	—	Right	7.5	Smooth surface	Destructive and nodular invasion	Left	Invasion of tubal wall
2	40	HSIL†	0	0	1	Colonization of glands	NA	NA	NA	NA	NA	NA
3	64	SCC	IB1	1	1	Colonization of glands; "carpet-like"	—	—	—	—	Left	Cystically dilated tube with mucosal colonization
4	41	SCC	IIIB	1	1	Diffuse infiltration of endomyometrium	Right	7	Surface nodule, small	Parenchymal nodules	Right	Serosal and stromal invasion
5	63	SCC	IB2	0	1	Diffuse infiltration of endomyometrium	—	—	—	—	—	—
6	69	SCC	IVB	1	NA‡	NA	BL	2.2, 2.5	Surface nodules, solid	Parenchymal nodules	Right	Mass in lumen
7	45	SCC	IB2	1	1	Diffuse infiltration of endomyometrium	—	—	—	—	—	—
8	73	SCC	IIA2	1	1	Diffuse infiltration of endomyometrium	Left	2.0	Smooth surface	Parenchymal nodules	Right	Serosal and stromal invasion
9	56	SCC	IIB	1	1	Colonization of glands; "carpet-like"	—	—	—	—	—	—
10	44	SCC	IB2	1	1	Diffuse infiltration of endomyometrium with papillary growth	—	—	—	—	Right	0.3 cm focus of mucosal colonization, keratin granulomas
11	68	AC	IIA2	1	1	Diffuse infiltration of endomyometrium	—	—	—	—	Right	Mucosal colonization
12	49	AC	IIA2	1	1	Diffuse infiltration of endomyometrium with invasion into leiomyoma	Left	2.6	Mass on surface, solid	Expansile and invasive	Right	Mucosal colonization with Intraluminal lesion
13	62	AC	IB1	1	1	Diffuse infiltration of endomyometrium	—	—	—	—	—	—
14	43	AC	IB2	1	1	Diffuse infiltration of endomyometrium	—	—	—		—	—
15	45	AC	IB1	1	1	Colonization of endometrium including adenomyosis; "carpet-like"	—	—	—	—	Left	Mucosal colonization
16	40	AC	IIB	0	NA§	NA	Right	4.0	Smooth	Small surface nodule with glands in mucin pools	Right	Mucosal colonization
17	48	AC	IIB	1	1	Colonization of endometrium with deep myometrial invasion	—	—	—	—	BL	Papillary, exophytic masses in paratubal soft tissue
18	44	AC	IIA2	0	1	Colonization of endometrium, papillary, villoglandular, eosinophilic; "carpet-like"	BL	8.0, 2.8	Surface nodules, solid	Surface nodules, papillary, expansile	Right	Mucosal colonization
19	41	AC	IVB	0	1	Colonization of endometrium, exophytic papillary; "carpet-like"	BL	15, 16.2	Nodular fungating tumor on surface	Expansile and infiltrative	Left	Small serosal implants
20	37	AC	IB1	0	0	—	—	—	—	—	Left	Mucosal colonization

*HIV-positive patient with history of HSIL presented with widely metastatic SCC.
†Completion hysterectomy at time of trachelectomy for HSIL at endocervical margin.
‡No hysterectomy performed, adnexa removed at time of exploratory laparotomy.
§Adnexa removed for diagnostic purposes, clinically high stage.
0 indicates absent; 1, present; AC, adenocarcinoma; BL, bilateral; FT, fallopian tube; HSIL, high-grade squamous intraepithelial lesion; NA, not assessed; SCC, squamous cell carcinoma.

Interestingly, 4 of the 10 patients with AC were originally diagnosed with endometrial endometrioid AC at outside hospitals (Patients 12, 13, 14, 18). Three had diffuse infiltration of the endometrium and myometrium, whereas 1 (Patient 18) had mucosal colonization of the endometrium spreading in a lateral "carpet-like" pattern. This patient's tumor also had a papillary/villoglandular growth pattern with abundant eosinophilic cytoplasm, truly mimicking an endometrial endometrioid AC. Two of the cases showed endocervical AC *in situ* in the cervix. Immunohistochemical studies had been performed on all 4 cases during routine work-up and all were found to be diffusely positive for p16, at least focally positive for monoclonal CEA, negative for vimentin, and no more than focally positive for estrogen receptor (ER) or progesterone receptor (PR)—consistent with endocervical AC. Of note, Patient 13 was originally diagnosed with endometrial endometrioid AC and presented to our institution with a mesenteric cyst 7 yr posthysterectomy. Immunohistochemistry performed on that cyst was consistent with endocervical AC, and, in addition, the glands lining the cysts were positive for high-risk HPV by HPV *in situ* hybridization (ISH) (Ventana INFORM HPV III). Comparison of the original hysterectomy to the cyst showed that they were the same tumor.

Corpus Involvement by AC

Corpus involvement was characterized by tumor colonizing endometrial mucosa which in some cases extended into the myometrium. Of the 10 ACs, 8 involved the corpus, 6 of which also involved the adnexa. AC involved endometrial mucosa in all cases and 5 also involved the myometrium. The following patterns of endometrial mucosal involvement were noted: villoglandular and cribriform glands replacing the vast majority of existing endometrial glands such that it resembled primary endometrioid AC of the endometrium (Fig. 1); endocervical AC colonizing endometrium with underlying normal endometrial glands and stroma such that it resembled complex atypical hyperplasia (Fig. 2); involvement of adenomyosis by endocervical AC maintaining a lobulated outline (Fig. 3). The myometrial involvement was usually extensive with deep invasion into the wall associated with large cervical masses.

Corpus Involvement by SCC/HSIL

SCC involved the uterine corpus in all 7 cases where the corpus was assessed, 4 of which had concurrent adnexal involvement. In all but 2 cases, SCC involved both the endometrium and myometrium and when the myometrium was involved, it was always in a diffusely infiltrative pattern with deep invasion and obliteration of the endometrial mucosa. The primary tumors were large (>4.0 cm) or deeply invasive into the cervical wall with direct extension into the corpus. Tumor invaded endometrial stroma, sometimes surrounding individual native endometrial glands (Fig. 4A) as well as colonizing them (Figs. 4B, C). These appeared to be a result of direct extension from the cervix and in 1 case, from tumor invading the deep myometrium with upward migration toward the endometrial lining. Two cases showed only colonization of endometrium with involvement of

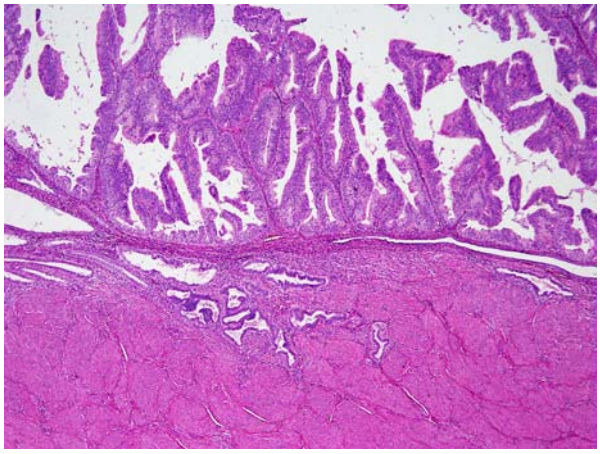

FIG. 1. Endocervical adenocarcinoma replacing endometrium resembling primary endometrioid adenocarcinoma (40 ×).

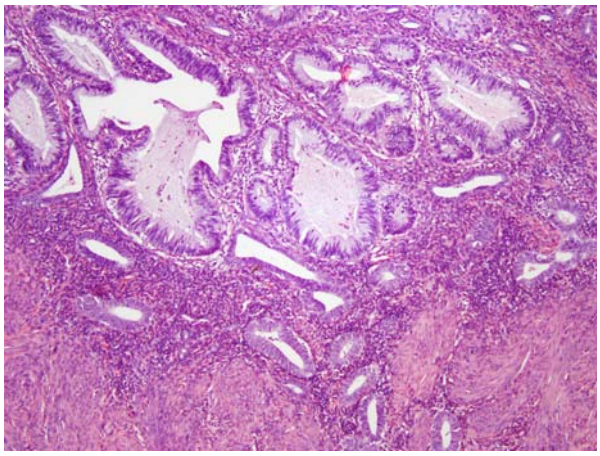

FIG. 2. Endocervical adenocarcinoma colonizing endometrial glands resembling complex atypical hyperplasia; notice benign endometrial glands of basalis beneath neoplastic glands (40 ×).

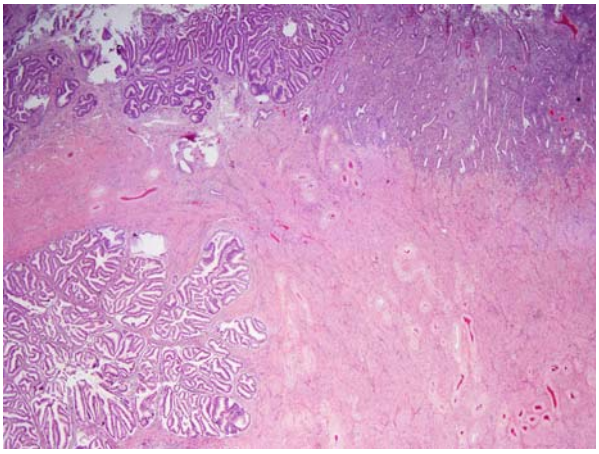

FIG. 3. Endocervical adenocarcinoma involving adenomyosis in myometrium with retained lobular configuration of glands; adenocarcinoma also colonizes endometrium in top left corner (20 ×).

glands in a "carpet-like" fashion, similar to that seen in AC (Fig. 5). The 1 HSIL involving the corpus showed focal gland colonization in the endometrium, similar to the common pattern of HSIL colonizing native endocervical glands.

Adnexal Involvement by AC

Four of 10 endocervical AC had ovarian metastases, synchronous in all cases. The ovarian tumors ranged in size from 2.6 to 16.2 cm, 2 bilateral, 2 unilateral, with 1 case showing bilateral ovaries >10 cm (all other involved ovaries were no greater than 8 cm). Three cases had visible surface nodules and the remaining case had a smooth ovarian surface. All showed a mostly solid cut surface. The ovarian tumors showed confluent papillary and cribriform glands with expansile growth. Cribriform structures were characterized

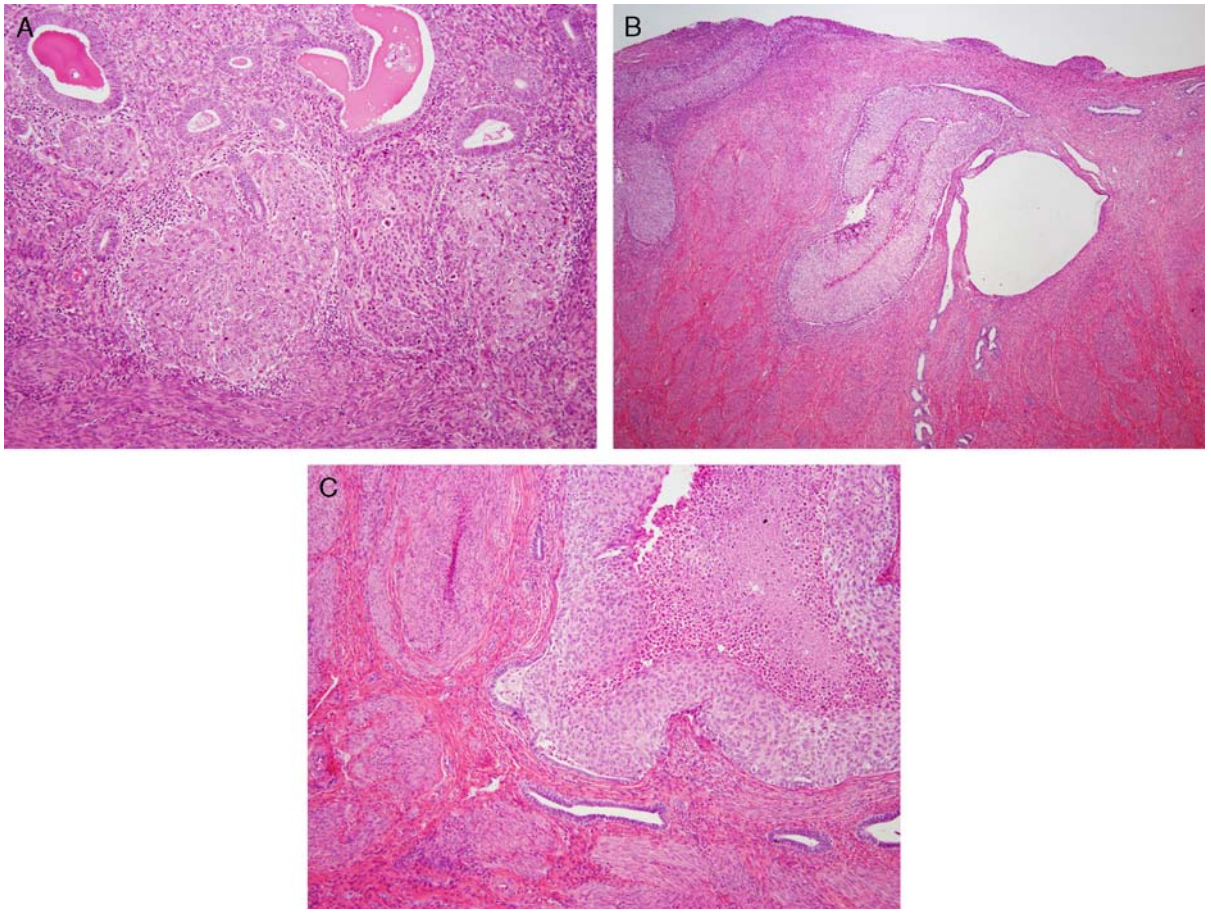

FIG. 4. Squamous cell carcinoma (SCC) involving endometrium; (A) invading endometrial stroma and surrounding native endometrial glands (100 ×); (B) SCC completely replacing (40 ×), and (C) colonizing (100 ×) endometrial glands.

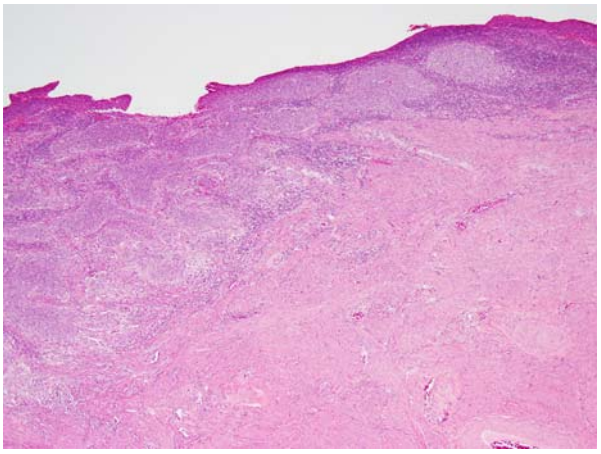

FIG. 5. Carpet-like involvement of endometrium by squamous cell carcinoma (40 ×).

by rigid and round lumens (Fig. 6). In 1 case (Patient 19) broad based papillae with hierarchical branching was also noted, very closely recapitulating the typical architecture of ovarian borderline tumors (Fig. 7A). Focal areas even resembled micropapillary serous borderline tumor with elongated tufts of tumors cells unsupported by fibrovascular cores (Fig. 7B). Occasionally, the epithelium lining the broad papillae became attenuated with minimal atypia and apocrine cytoplasm, truly resembling a cystadenofibroma (Fig.7C). Immunohistochemistry performed on both ovaries showed that the tumor was diffusely and strongly positive for p16 and monoclonal CEA, negative for vimentin and PR, with weak patchy ER reactivity. High-risk HPV was detected by HPV ISH as well (Ventana INFORM HPV III). Careful examination of the histology revealed areas with more columnar epithelium harboring easily identified mitoses and apoptotic bodies, although these features were not prominent. One case had only a small nodule of neoplastic glands in mucin pools on the ovarian serosa (Fig. 8). In all of the cases the tumors showed "endometrioid" morphology displaying tall columnar cells with elongated nuclei and only focal mucinous differentiation. High-power examination revealed characteristic features of endocervical AC—hyperchromatic elongated nuclei, moderate atypia with numerous apical mitoses, and apoptotic bodies (Fig. 9).

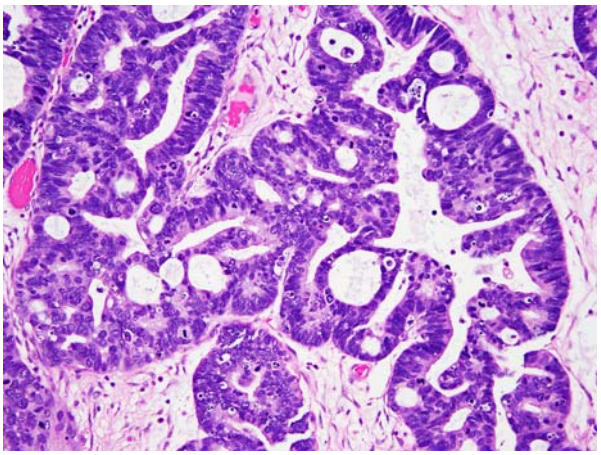

FIG. 6. Characteristic features of endocervical adenocarcinoma with confluent papillary glands and cribriform structures with rigid round lumens (100 ×).

Fallopian tube metastasis by endocervical AC was seen in 8 of the 10 cases and the lesions were all microscopic, measuring between 0.1 and 0.4 cm, except for 1 case (Patient 17). This patient presented with vaginal discharge and large adnexal masses. She was thought to have a fallopian tube primary carcinoma and showed papillary, exophytic masses in the paratubal soft tissue. This was the only case of bilateral tubal involvement; all others were unilateral and either microscopically colonized preexisting fallopian tube epithelium simulating serous tubal intraepithelial carcinoma (STIC) on low power (6 cases) (Figs. 10A, B) or had small serosal implants (1 case). Some showed papillary tufting and slit-like spaces more typical of high-grade serous carcinomas with high nuclear grade (Fig. 10C). The lesions were multifocal and ranged from flat (Fig. 10D) to cribriform (Fig. 10E) to papillary (Fig. 10F). Focal stromal invasion was occasionally seen (Fig. 10G). Closer inspection revealed intracytoplasmic goblet-like mucin in some of the cells and overall the tumors resembled the cervical tumor (Fig. 10H).

Adnexal Involvement by SCC/HSIL

Three of 8 patients with cervical SCC had ovarian involvement, whereas 1 patient with cervical HSIL showed invasive SCC in one ovary. Ovarian and/or fallopian tube involvement was evident at the time of diagnosis in all but 1 case (Patient 10) and LVI in the periadnexal soft tissue was often present. Ovarian involvement was unilateral (3) and bilateral (1) with ovarian sizes ranging from 2 to 7.5 cm. One case showed tumor in the left ovary and the right periadnexal soft tissue. Two of the 4 cases had grossly visible ovarian surface nodules, whereas the other 2 had smooth surfaces without evident tumor. All of the cases revealed nodules of SCC replacing normal ovarian parenchyma with stromal invasion (Fig. 11).

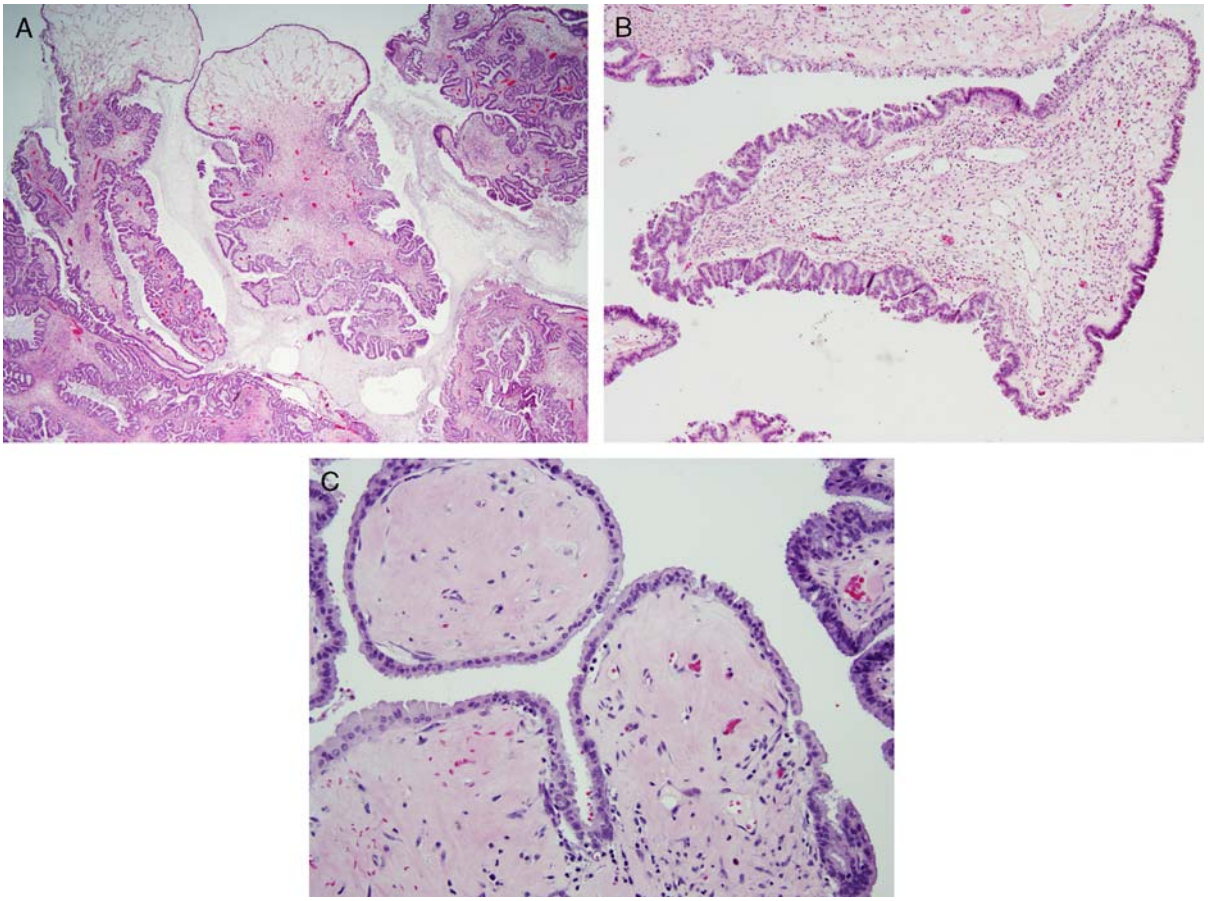

FIG. 7. Endocervical adenocarcinoma involving ovary and mimicking borderline tumor. (A) Broad based papillae with hierarchical branching and epithelial tufting (40 ×); (B) elongate tufts of tumor cells unsupported by fibrovascular cores, resembling micropapillary borderline tumor (100 ×); (C) flat epithelial lining of tumor cells resembling cystadenofibroma; notice mitotic figure and intracytoplasmic mucin in upper right corner (100 ×).

The fallopian tubes were involved in 6 SCC, all unilateral. Lesions were small and measured < 1 cm in 3 cases. The other 3 cases showed grossly enlarged fallopian tubes. In 1 case, the tumor colonized the mucosa of a cystically dilated fallopian tube, resulting in a 9-cm cystic mass (Patient 3). There was no stromal invasion and the cystically dilated tube had the appearance of an *in situ* SCC (Fig. 12A). The interesting thing about this case is that the primary cervical lesion was predominantly HSIL with only focal stromal invasion; however, there was extensive "carpeting" of the endometrium by SCC without myometrial invasion (Fig. 12B). The ipsilateral ovary was not involved except in the form of LVI in the periadnexal vessels. A second case had an intraluminal tubal mass with replacement of the tubal mucosa (Patient 6) (Fig. 13). The third was 1 case of HSIL in an HIV-positive patient who presented with invasive SCC in the ovary and fallopian tube (Fig. 14A). There was an area of inflammation associated with her cervical HSIL that suggested possible regression of an invasive tumor (Fig. 14B). There was no other obvious source of invasive SCC. Two cases had nodules of SCC surrounding the fallopian tube. One case showed keratin granulomas on the tubal serosa with a minute focus of SCC colonizing the tubal epithelium beneath the granuloma (Fig. 15A). This focus was highlighted by diffuse strong p16 reactivity (Fig. 15B).

DISCUSSION

Although there are reports describing the morphologic features of cervical AC and SCC metastatic to ovaries, little is written about involvement of fallopian tubes and direct extension to the uterine

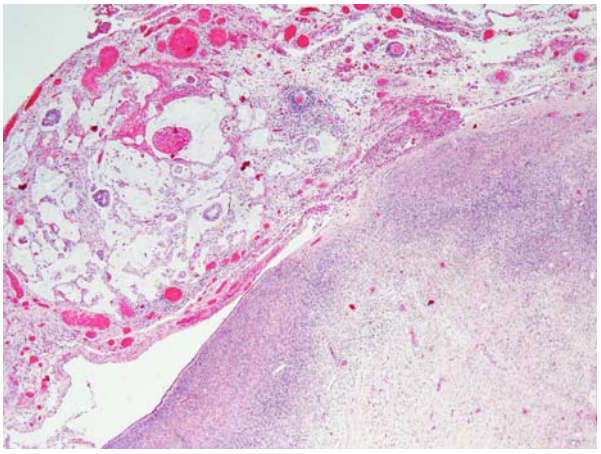

FIG. 8. Metastatic endocervical adenocarcinoma with extravasated mucin on ovarian surface (40 ×).

corpus. The 20 cases presented in this study illustrate the patterns of ovarian and/or fallopian tube and endometrial involvement by cervical SCC and AC. Cervical SCC and AC infrequently metastasize to the adnexa (2,3) and the reported cases in the literature mainly describe ovarian involvement (5–8).

Endocervical AC metastatic to the ovary tends to simulate primary ovarian surface epithelial neoplasms (7,8); they frequently exhibit mucinous and endometrioid differentiation, which often makes them difficult to distinguish from primary ovarian borderline tumors and carcinomas (9,10). The majority of synchronous ovarian and endocervical tumors were previously interpreted as independent neoplasms (11–13). Primary ovarian tumors can be distinguished from metastatic tumors to the ovaries when they exhibit characteristic microscopic and gross appearances. Previous studies have shown that a simple algorithm using tumor size and laterality (bilateral tumors of any size, or unilateral tumor < 10 cm = metastatic; unilateral tumor ≥ 10 cm = primary) can distinguish between primary and metastatic mucinous tumors involving the ovary (14–17). Primary ovarian carcinomas arising in association with borderline tumors frequently show expansile or confluent glandular pattern of invasion as opposed to destructive stromal invasion. In contrast, metastatic tumors to the ovaries are usually characterized by bilaterality, small ovarian size, ovarian surface involvement, and an infiltrative pattern of stromal invasion. There have been reports of various AC, including colorectal and endocervical tumors, which show gross and microscopic features suggestive of primary ovarian tumors (7,16,18–20).

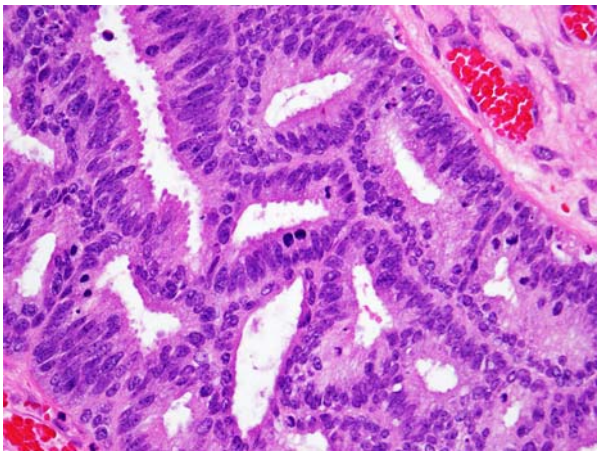

FIG. 9. Mucin-depleted "endometrioid" appearance of metastatic endocervical adenocarcinoma with numerous luminal mitotic figures and abundant apoptotic bodies (400 ×).

Of 10 AC, 4 involved ovaries and most simulated ovarian primaries morphologically. They showed an endometrioid appearance with confluent glandular growth pattern at low-power magnification that could be mistaken for endometrioid ovarian primary tumors. High-power evaluation revealed elongated, hyperchromatic nuclei with mucinous areas at least focally and the typical histologic features encountered in endocervical ACs: prominent apical mitoses and apoptotic bodies. Tumors exhibiting these appearances may be misdiagnosed as endometrioid/mucinous borderline tumor with intraepithelial carcinoma. To further complicate the issue, while 2 of the ovarian metastases were unilateral, there was 1 case with bilateral ovaries that measured > 10 cm (15 and 16.2 cm), again raising the question of an ovarian primary (16). It is important to remember that bilaterality is not a common feature of cervical AC metastatic to ovaries, and often they can present as masses > 10 cm (16). One of the clues that this is not a typical primary ovarian tumor is the discordance between the well-differentiated architecture and higher-grade cytology. Only one of our cases showed the destructive pattern of invasion usually associated with a metastatic process. In our cases, most of the cervical carcinomas had visible lesions and were deeply invasive into the cervical stroma. This is in contrast with what Elishaev and Ronnett (7,19) have previously reported in their cervical AC cases, of which many were only superficially invasive. It is a well-known fact that endocervical AC commonly

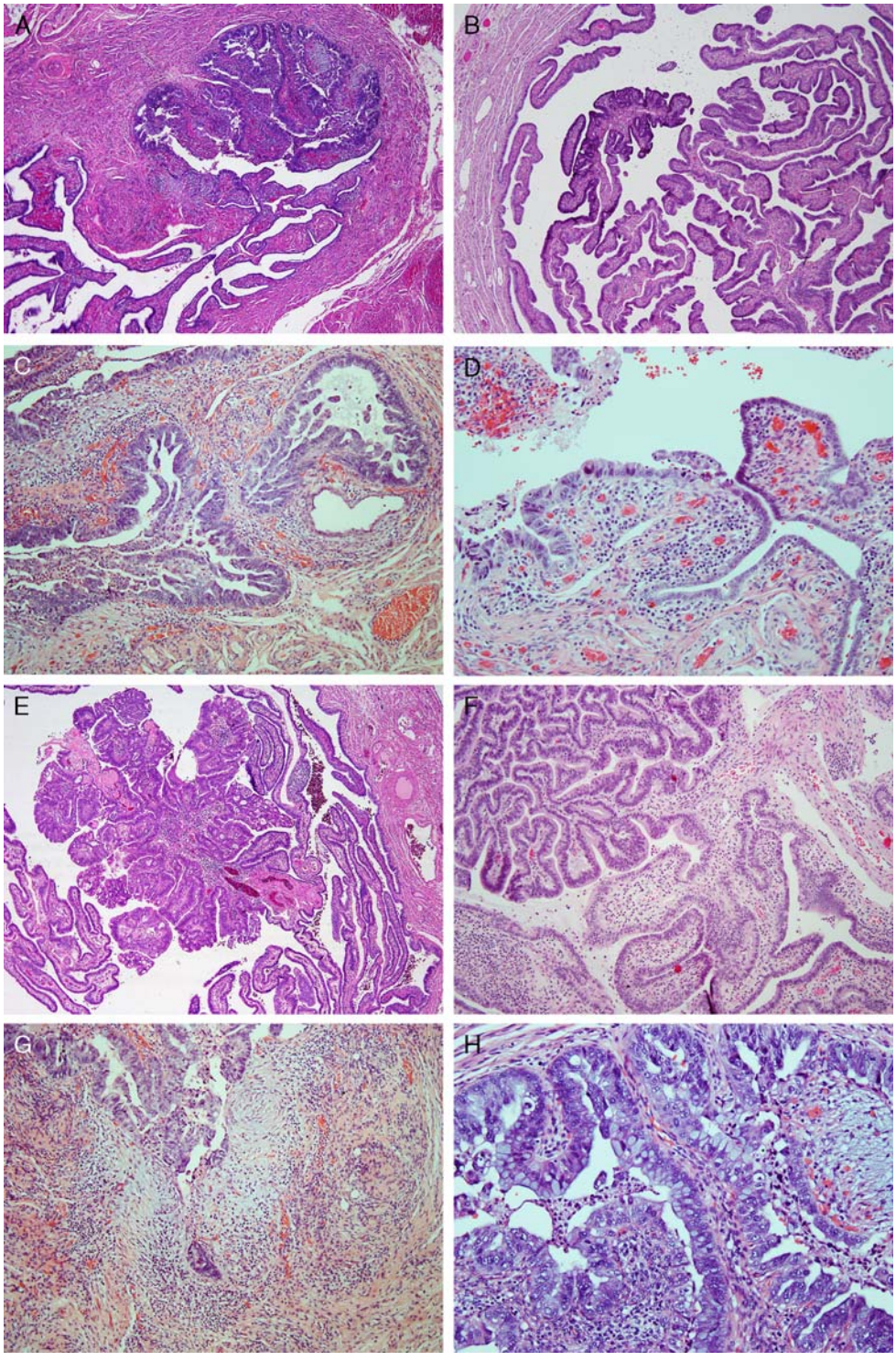

FIG. 10. Endocervical adenocarcinoma (AC) metastatic to fallopian tubes. (A and B) 40 × mucosal colonization by AC resembling serous tubal intraepithelial carcinoma (STIC); (C) 100 × papillary tufting and slit-like spaces with high nuclear grade mimicking serous carcinoma; (D) 400 × flat; (E) 40 × cribriform; and (F) 100 × papillary appearance of endocervical AC in fallopian tube mucosa; (G) 100 × focal stromal invasion of fallopian tube wall; (H) 400 × intracytoplasmic mucin goblets of endocervical AC.

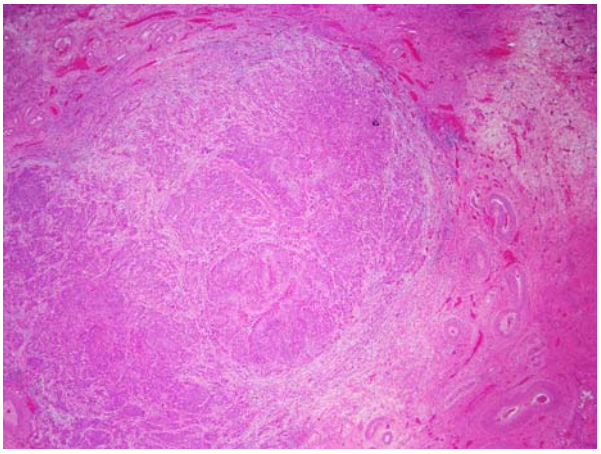

FIG. 11. Nodule of metastatic squamous cell carcinoma (SCC) involving ovarian parenchyma (20 ×).

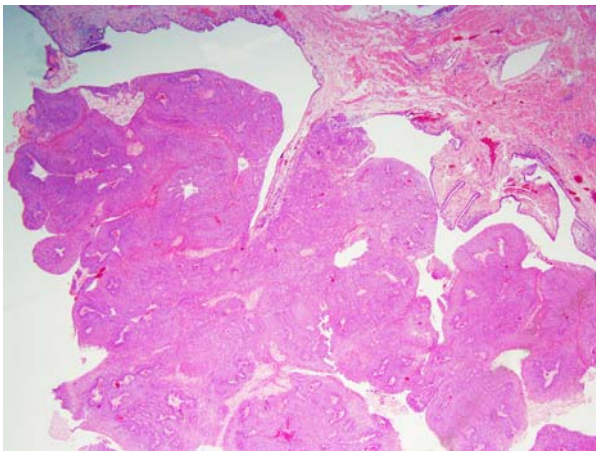

FIG. 13. Intraluminal mass of metastatic squamous cell carcinoma (SCC) involving fallopian tube and replacing tubal mucosa (40 ×).

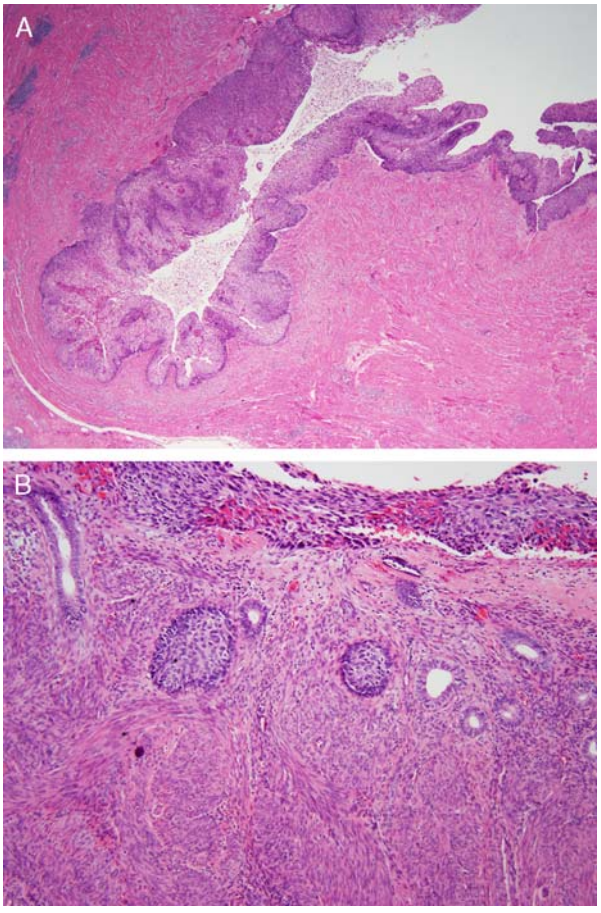

FIG. 12. (A) 40 × cystic dilatation of fallopian tube colonized by squamous cell carcinoma (SCC) in a patient with predominantly high-grade squamous intraepithelial lesion and extensive (B) 100 × carpet-like growth into endometrium with replacement of endometrial glands.

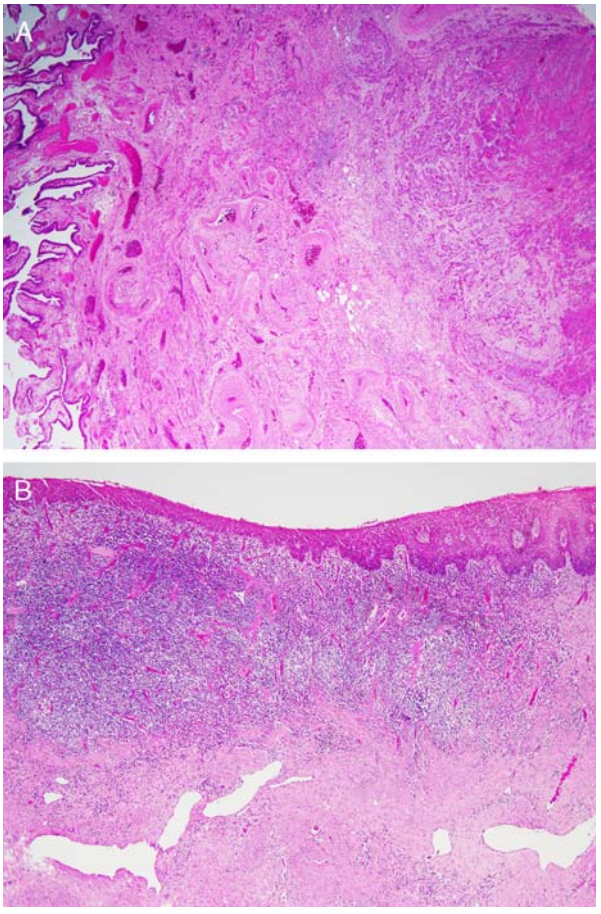

FIG. 14. (A) 20 × metastatic squamous cell carcinoma (SCC) with invasion into fallopian tube wall in an HIV-positive patient with high-grade squamous intraepithelial lesion and area of inflammation in cervix; (B) 40 × possibly representing regressed invasive tumor.

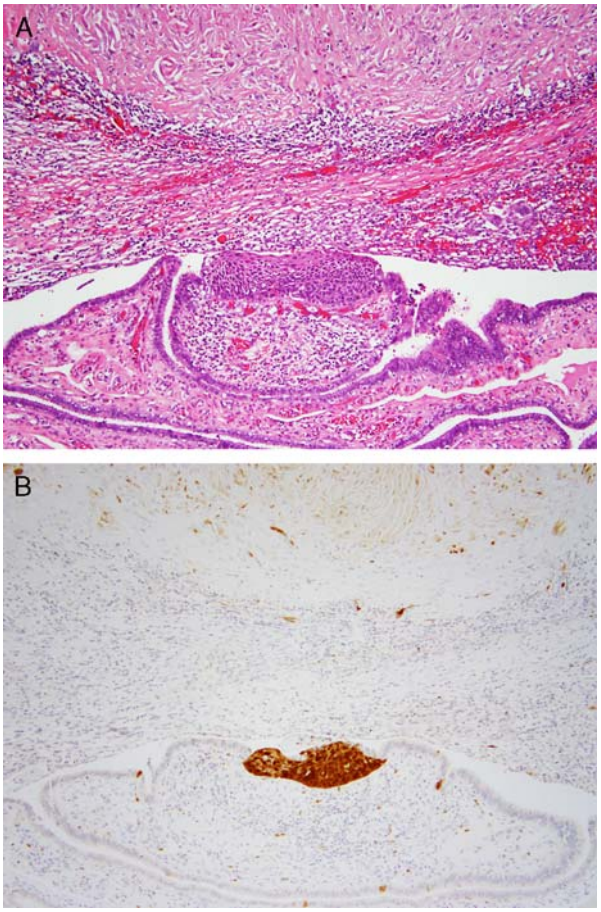

FIG. 15. (A) 400 × metastatic squamous cell carcinoma (SCC) with focal mucosal colonization of fallopian tube and associated keratin granuloma highlighted by diffuse strong (B) 400 × CINtec p16 (Ventana, Tucson, AZ).

exhibits endometrioid and mucinous differentiation (9,21), pitfalls that may lead to a misdiagnosis of such tumors as primary ovarian endometrioid/mucinous neoplasms. It is therefore important to evaluate these lesions carefully such that the presence of cytologic features suggestive of endocervical AC (i.e. elongated nuclei with apical prominent mitoses and apoptotic bodies) should prompt a search for a primary cervical tumor which can be excluded with the aid of clinicopathologic correlation and/or immunohistochemistry.

Most of the cases with fallopian tube involvement by endocervical AC exhibited microscopic lesions which were limited to the fallopian tube epithelium with no stromal invasion. Endocervical AC colonized preexisting fallopian tube epithelium, and at low-power magnification, epithelial stratification and nuclear hyperchromasia were seen, simulating STIC. However, closer inspection revealed tall, stratified, hyperchromatic nuclei with prominent apical mitoses and apoptotic bodies. We did not use immunohistochemistry in this study, but when in doubt one can perform immunohistochemistry for p53 and HPV ISH when this differential diagnosis arises: endocervical AC are characterized by positive HPV ISH and no p53 overexpression, whereas STIC exhibits p53 overexpression or null pattern and negative HPV ISH. It should be noted that there are several commercially available HPV ISH tests, some of which are less sensitive than others, in particular for AC (22,23). Immunohistochemistry for p16 in this setting is not helpful as both high-grade serous tumors and HPV-associated cervical cancers are typically diffusely positive for this marker.

In all cases of endocervical AC secondarily involving the endometrium, the tumor colonized or obliterated normal endometrial glands. Endocervical AC frequently demonstrate "endometrioid" morphology and if there is dominant uterine corpus involvement by endocervical AC it can lead to misclassification as primary endometrial AC with cervical extension or even complex atypical hyperplasia if present on an endometrial biopsy (24). In our cases, this scenario was observed in 4 cases where the patient was initially diagnosed as having an endometrial primary.

It is rare to encounter metastatic cervical SCC or AC in the adnexa. Most cases of cervical SCC secondarily involving ovaries in this study had a nodular appearance at low-power magnification. Although only 1 of the 4 cases had bilateral ovarian tumors, they all showed areas of destructive stromal invasion suggestive of a metastatic process and 3 exhibited ovarian surface nodules. Fallopian tube involvement by SCC was seen in the form of carcinoma replacing and colonizing fallopian tube epithelium and also in the form of nodules of SCC surrounding the tube. Most of our cervical SCC were deeply invasive with a visible lesion. We had 1 case of adnexal/endometrial involvement by SCC limited to superficial cervical invasion, which has been described by others (25,26). One patient had HSIL only in the cervix with invasive SCC in the ovary and fallopian tube presenting as a large pelvic mass. There is one other report of ovarian SCC occurring in a setting of microinvasive SCC 8 yr after the original diagnosis (27).

As previously reported, the vast majority of cases of adnexal involvement occurred in the setting of advanced stage cervical carcinoma with extrauterine

involvement or large bulky primary tumors. However, there were cases of early-stage disease and even cases of noninvasive squamous carcinoma that extended into the uterine corpus and adnexa. Specifically, the "carpeting" growth pattern of tumor spreading superficially and laterally along the endometrium was seen in both squamous and ACs with tumor involving adnexa without obvious myometrial infiltration or LVI. This phenomenon should be taken into consideration when contemplating ovary and fallopian tube-sparing hysterectomies in patients with minimal or no invasive disease. One patient (Patient 1) with only cervical HSIL showed diffusely metastatic SCC including extensive involvement of the ovary. She was HIV-positive and was found to have a focus in the cervix with an exuberant lymphocytic reaction in the stroma, as is typically seen in regressing melanomas. This may have represented regressed invasive carcinoma, although there was no definitive evidence to support this.

In summary, we have presented a relatively large study of cervical carcinomas that secondarily involve the corpus, ovaries, and fallopian tubes. There is overlap between the histologic appearances of these tumors and primary carcinomas arising at these sites, and erroneous assignment of the primary tumor site may lead to inappropriate and potentially harmful treatment. Careful morphologic evaluation, allied with clinicopathologic correlation, and the judicious use of ancillary tests such as immunohistochemistry and ISH, will help avoid diagnostic pitfalls and allow accurate diagnosis.

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