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Abstract:

Objective: Gastric-type endocervical adenocarcinoma (GAS) is an uncommon type of endocervical adenocarcinoma that is not associated with human papillomavirus (HPV) infection. This diagnosis is relatively rare and may portend a worse prognosis than usual-type endocervical adenocarcinoma. Subtle morphologic features make it an underrecognized diagnostic challenge. Study of the cytologic features of individual cases is valuable in order to increase awareness of this entity.

Methods: The pathology database of our institution was searched for the diagnosis of GAS and all cytologic and surgical specimens for each patient were reviewed. The original cytologic interpretation was compared to a retrospective central review interpretation. Clinical history and follow up results were obtained from the electronic medical record.

Results: Four cases of GAS were identified. The findings on initial cervical cytology varied, with GAS found in both patients with negative cervical cytology and those with atypical glandular cells. Cytologic findings included endocervical cells arranged in three-dimensional clusters and honeycomb sheets with abundant vacuolar cytoplasm, and in two patients, moderate nuclear atypia with irregular nuclear membranes, coarse chromatin, hyperchromatic nuclei, and prominent nucleoli. In one patient, GAS was incidentally discovered via thorough sampling of a cystic lesion in the superior portion of the endocervical canal.

Conclusions: GAS is an aggressive HPV-independent type of endocervical adenocarcinoma with subtle morphologic features and, as our study shows, varying clinical presentation. Given the aggressive nature of GAS and the difficulties in initial diagnosis, increased awareness of this entity among pathologists is crucial.

Keywords: Gastric-type endocervical adenocarcinoma, cervical cytology, human papillomavirus.

Abbreviations: Human papillomavirus = HPV. Endocervical curettage = ECC. Usual (HPV-related) endocervical adenocarcinoma = UEA. Gastric-type endocervical adenocarcinoma = GAS. Atypical glandular cells = AGC.

Introduction:

Endocervical gastric-type adenocarcinoma (GAS) is an aggressive, uncommon, HPV-independent type of endocervical cancer that can pose diagnostic difficulty in both cytologic and

surgical sampling specimens[1-3]. The reported cytologic diagnostic features of GAS are subtle and include monolayered and honeycombed sheets of cells with vacuolar or foamy cytoplasm, vesicular nuclei with distinct nucleoli, and minimal to absent mitotic activity[4, 5]. Yellow mucin has been reported as a diagnostic clue in some studies[6] but not in others[7]. GAS is typically negative for p16 by immunohistochemistry[8]. Since many of these features overlap with those of benign reactive alterations such as microglandular hyperplasia, lobular endocervical hyperplasia, or deep Nabothian cysts, GAS may be misinterpreted as a benign entity despite its predilection to present with advanced stage involvement of the pelvis and abdomen. Unlike usual HPV-related endocervical adenocarcinomas (UEA), GAS tumors are often located in the upper endocervix and typically do not form well-demarcated masses[2]. In the current era of HPV vaccination, a relative increase in non-HPV-associated endocervical adenocarcinomas may arise. Given that GAS is not HPV-associated, these cases will not be detected by HPV-only screening programs, leaving cytology as an important possible diagnostic opportunity.

Here we present four cases of GAS diagnosed over two years at a local general hospital. GAS is a diagnostic challenge due to its rarity, subtle histologic and cytologic features, and lack of association with HPV. The aim of this study was to evaluate the cytologic features of GAS in comparison to reported features of GAS with an emphasis on diagnostic pitfalls. Awareness of the morphologic features of GAS will enhance pathologists' ability to recognize this difficult tumor.

Material and Methods:

Patient Selection:

After obtaining IRB approval, the pathology database was searched for the diagnosis of GAS in cytologic and/or surgical pathology specimens at Zuckerberg San Francisco General Hospital from 2000 to 2018. All relevant cervical cytology and surgical specimens for each patient were reviewed. The original interpretation on cytology was compared to a retrospective central review interpretation performed by three cytopathologists (PV, NG, TD). Clinical history and follow up results were obtained from the electronic medical record.

Cytology analysis:

Cervical cytology samples were prepared using SurePath (BD diagnostics). All cytology results were reported according to The Bethesda System terminology (TBS).

Immunohistochemistry (IHC):

The following immunohistochemical stains were performed on available cytology cell blocks (p16 on one case) and surgical specimens (three cases) as part of the clinical work up. All four patients had MUC6 and p16 stains performed on surgical specimens as part of the clinical work up, and three of the patients also had ER stain. The immunohistochemical stains, clones, and dilutions are as follows: P16: clone E6H4, no dilution. ER: clone SP1, dilution 1:100. CEA: monoclonal, dilution 1:200. Vimentin: clone V9, dilution 1:1000. Ki67: clone SP6, dilution 1:50. Napsin: clone MRQ-60, dilution: 1:100. P53: clone DO-7, dilution 1:100. CK7: clone OV-TL 12/30, dilution 1:200. CK20: Clone Ks20.8, dilution 1:100. MUC6 clone: CLH5; dilution 1:200. HNF-1 clone: polyclonal; dilution 1:200.

Results (Case Series)

Four patients with a diagnosis of GAS were identified, all diagnosed between 2017 and 2018. Cervical cytology and surgical specimens, including cervical biopsies and LEEP specimens were available for all four patients. Hysterectomy specimens were available for three patients. One patient's radical hysterectomy was aborted when a pelvic lymph node metastasis was identified on frozen section; however, she did undergo bilateral salpingo-oophorectomy.

Patient 1:

The patient was a 36-year-old woman with no prior abnormal cervical cytology (Table 1). The patient underwent hysterectomy due to dysmenorrhea, with ultrasound showing adenomyosis. Her most recent cervical cytology prior to hysterectomy was interpreted as negative for intraepithelial lesion by the original pathologist; retrospective central review similarly showed a few clusters of benign endocervical cells in a background of many squamous cells (Figure 1A, Table 2). On careful gross examination of her hysterectomy specimen, a 2 cm ill-defined, soft, tan lesion composed of multiple small cysts filled with mucinous material was identified in the proximal endocervical canal/lower uterine segment (Figure 1B). On histologic exam, the lesion was shown to be GAS, with the tumor infiltrating deep into the cervical stroma, eliciting focal desmoplasia. The tumor cells had abundant mucinous cytoplasm and vesicular nuclei with prominent nucleoli. Scattered mitoses were identified. On the surface, only focal mild atypia was present, characterized by nuclear pseudostratification and moderate hyperchromasia. The tumor was negative for p16 and positive for

MUC6 IHC. The patient was FIGO stage IB2, elected surveillance, and has had no recurrence as of seventeen months after hysterectomy.

Patient 2:

The patient was a 60-year-old woman with previously negative cervical cytology who presented with post-coital bleeding (Table 1). Her two subsequent cervical cytology specimens consisted almost entirely of endocervical cells and were interpreted by the original pathologist as unsatisfactory due to scant squamous component (Figure 2A-B, Table 2). On re-review, the striking feature of this case was the increased number of normal-appearing endocervical cells. The smear showed numerous tall and columnar endocervical cells with occasional three-dimensional clusters. The cells demonstrated abundant vacuolar and foamy cytoplasm, focal goblet cells, feathering and mild nuclear atypia with vesicular nuclei and conspicuous nucleoli, not reaching the threshold for a diagnosis of AGC or AIS (Figure 2A-B, Table 2). Subsequent endocervical curettage (ECC) and cervical biopsy showed GAS (Figure 3A), with positive MUC6 IHC (Figure 3B) and negative p16, ER, CEA, and vimentin. While the biopsy was fragmented, surface tumor cells showed mild atypia with pseudostratification, hyperchromasia, and abundant vacuolated cytoplasm. Her subsequent hysterectomy was aborted due to an intraoperative frozen section finding of a left obturator lymph node with metastatic GAS (Figure 4A). However, a myomectomy and bilateral salpingo-oophorectomy were performed and metastatic GAS was identified in one fallopian tube. She was treated with chemotherapy and radiation. One year after the aborted hysterectomy, she presented with an enlarged left supraclavicular lymph node; fine needle aspiration biopsy showed metastatic GAS (Figures 4B-C).

Patient 3:

The patient was a 61-year-old woman whose initial cervical cytology showed atypical glandular cells (AGC) (Figure 5A-D, Tables 1-2). Repeat cervical cytology and subsequent ECC showed atypical endocervical epithelium with a differential of reactive versus neoplastic, given the prior diagnosis of AGC on cytology. On retrospective review, the cervical cytology was best classified as AGC, favor neoplastic, with endocervical cells arranged in three dimensional clusters (Figure 5A) and honeycomb sheets. The endocervical cells had abundant vacuolar foamy cytoplasm, markedly irregular nuclear outlines, hyperchromasia, focal apoptosis, and feathering (Figure 5B-D). A

brown/yellow hue in the mucin was also seen (Figure 5B). On subsequent endocervical and endometrial biopsy the endocervical epithelium was interpreted as benign with tubal metaplasia. She then underwent two cervical cone biopsies. The first showed GAS at least in situ, with positive CK7 and negative CK20 IHC supporting endocervical origin, and positive MUC6, negative p16, and negative Napsin supporting GAS. Ki67 showed a proliferation index of less than 5%. The second cervical cone biopsy showed invasive GAS with a positive deep margin. Hysterectomy showed invasive GAS (Figure 5E) with lymphovascular invasion, FIGO stage IB3. In areas with underlying invasive tumor, the surface endocervical cells showed moderate atypia with pseudostratification, irregular nuclear membranes, abundant vacuolated cytoplasm, and scattered mitoses. Endocervical cells appeared normal in areas with no underlying tumor. She underwent radiation therapy and had no recurrence as of 29 months.

Patient 4:

The patient was a 55-year-old woman with previously negative cervical cytology, followed by a cervical cytology four years later showing AGC (Tables 1-2). On re-review, the cervical cytology (Figure 6A-C) was best classified as AGC, favor neoplastic, with abundant endocervical cells mainly in dense three-dimensional clusters, with pseudostratification, vacuolated and foamy cytoplasm, irregular nuclear outlines, coarse chromatin, and prominent nucleoli. Scattered goblet cells and occasional mitoses were present. Abundant inflammation was present in the background, suggestive of a diathesis. A cell block (Figure 6D) was prepared from the residual cervical cytology specimen; the atypical glandular cells were negative for p16 and positive for CEA (Figures 6E-6F). Subsequent cervical polypectomy, ECC, and endometrial biopsy all showed at least in situ GAS, with IHC results as follows: patchy MUC6 and vimentin, positive CEA, and negative p16 and ER. Later cervical cone biopsy and hysterectomy both showed invasive GAS, FIGO stage IB2. On her hysterectomy specimen, the surface was predominantly denuded. However, in areas with underlying invasive tumor and intact surface, the surface endocervical cells showed moderate atypia, with pseudostratification, high nuclear to cytoplasmic ratios, hyperchromasia, hobnailing, and eosinophilic cytoplasm. The patient did not undergo chemotherapy or radiation and was free of recurrence as of 14 months.

The Peutz-Jeghers status of the four patients was not known.

Follow up

Follow up information was available in all four patients with follow up time ranging from six months to 42 months. The three patients who underwent hysterectomy had no recurrence; the patient whose hysterectomy was aborted due to metastatic disease received chemoradiation therapy but presented one year later with metastatic GAS in a left supraclavicular lymph node.

Discussion:

Gastric-type endocervical adenocarcinoma (GAS) is an aggressive and uncommon type of endocervical cancer[1]. By the most recently proposed classification, the International Endocervical Adenocarcinoma Criteria and Classification (IECC), which is based on etiology and biologic behavior[9], GAS is classified as a non-HPV-associated adenocarcinoma. GAS is relatively rare in Western countries but has been reported to be more common in Japan, where it accounts for approximately 20-25% of all endocervical adenocarcinomas[2]. GAS occurs across a wide age range, with reported ages ranging from the twenties to seventies[7]. The majority of GAS cases are sporadic, though some cases are associated with mutations in the STK11 tumor suppressor gene (Peutz-Jeghers syndrome)[10]. Next-generation sequencing of GAS has shown mutations in TP53, MSH6, CDKN2A/B, POLE, SLX4, ARID1A, STK11, BRCA2, and MSH2[11].

Unlike UEA, GAS tumors are often located in the upper endocervix. As a result of their highly infiltrative growth pattern, they typically do not form well-demarcated masses[2]. Commonly reported symptoms of GAS include irregular vaginal bleeding and vaginal discharge. These symptoms lack specificity as they are similar to those in patients with other types of endocervical pathologies; vaginal discharge, for example, can occur in benign entities such as lobular endocervical glandular hyperplasia (LEGH)[12].

Compared to UEA, GAS has worse outcomes, even at stage I, often presents at high stage, is relatively resistant to standard chemotherapy regimens[3, 13], and often metastasizes to unusual sites such as the omentum, peritoneum, adnexa, liver, brain, and bone[8, 13, 14]. The propensity for spread to these unusual sites is distinct from UEA, which typically do not metastasize from the pelvis until late in the course of the disease[14]. In one study[15], the disease-specific survival at 5 years for GAS patients was 42% versus 91% for UEA patients. In that study, the majority of patients with GAS presented at a high stage (stage II-IV) versus only 41% presenting at stage I[15].

GAS exhibits a range of microscopic morphology, with common features including distinct cell borders and abundant foamy or pale cytoplasm[16]. Well-differentiated forms of GAS, previously called minimal-deviation adenocarcinoma or adenoma malignum, can be deceptively bland, making accurate diagnosis difficult. The difficulty of an accurate diagnosis of GAS was highlighted in one study[16] in which of 20 submitted cervical biopsies, GAS was suspected by the submitting pathologist in only 5 (25%) of the cases. GAS often exhibits strong MUC6 expression by IHC[8, 17]. Unlike HPV-related cervical adenocarcinomas, which are diffusely positive for p16, GAS is typically negative or only focally positive for p16[8].

On cervical cytology specimens, GAS has been reported to show endocervical cells in monolayered and honeycomb sheets with well-defined cell borders, pale vacuolar and/or foamy cytoplasm, and vesicular nuclei with conspicuous nucleoli[4, 5, 7, 16, 18-20]. Peripheral palisading mimicking feathering has also been reported[18]. Yellow mucin has also been reported as a diagnostic clue for endocervical glandular lesions with gastric differentiation[6].

The cytologic features of GAS are challenging. We describe four cases of non-HPV associated (p16-negative) GAS. The range of clinical presentations and cervical cytology findings provides an overview of salient points about this entity and illustrates the difficulty in establishing an initial diagnosis.

Patient 1 had previous negative cervical cytology, confirmed on re-review, and GAS was only discovered on hysterectomy performed for abnormal uterine bleeding. Astute gross examination of her hysterectomy specimen revealed a 2 cm cystic lesion in the superior portion of the endocervical canal that was well sampled and shown to be GAS. The incidental finding of GAS in Patient 1 highlights the importance of careful initial gross exam of all hysterectomy specimens, and a low threshold for liberal sampling of cystic lesions resembling crowded Nabothian cysts. Her previously normal findings on cervical cytology is not entirely surprising since, like many GAS tumors, her tumor was located in the superior portion of the endocervical canal, an area not routinely sampled by cervical cytology[2].

For patient 2, who presented with post-coital bleeding, she had two previous cervical cytology specimens that were deemed unsatisfactory due to insufficient squamous component. However, both cervical cytology specimens consisted almost entirely of abundant mostly bland-appearing

endocervical cells with abundant vacuolar and foamy cytoplasm and scattered goblet cells, mild nuclear atypia, feathering and occasional three-dimensional clusters. The striking feature of this case was the increased number of endocervical cells similar in morphology to normal endocervical cells; focal minimal atypia was noticed only on retrospective review. The endocervical cells were arranged in sheets, strips, and as isolated cells. The cytomorphologic features on her cervical cytology did not fulfill criteria for a diagnosis of adenocarcinoma in situ (AIS) or AGC. However, her presentation supports the argument that further follow up with colposcopy and endocervical sampling could be considered for women without large ectropion who have abundant bland-appearing endocervical cells on cervical cytology.

For patient 3, atypical glandular cells were initially seen on cervical cytology. Re-review further confirmed these findings and was best classified as AGC favor neoplastic based on the nuclear atypia. However, on subsequent endocervical and endometrial biopsy the atypical glandular cells were interpreted as tubal metaplasia. While she was eventually diagnosed with GAS on ECC, the initial diagnosis of tubal metaplasia caused a delay in treatment.

For patient 4, her cervical cytology showed three-dimensional clusters of atypical endocervical cells, with occasional mitoses. By the time patient 4 presented at our institution and was found to have AGC on cervical cytology, patients 1-3 had already presented, and the diagnostic features of GAS were better known at our institution. Given the high suspicion for GAS, a cell block was prepared from her cervical cytology specimen, which showed that the atypical glandular cells were negative for p16. Soon after her cervical cytology with AGC she underwent ECC and endometrial biopsy which showed at least in situ GAS. For patient 4, her cancer may have been missed if she had only undergone HPV screening without cervical cytology, as GAS is not related to HPV infection.

In our four cases, we found a constellation of cytologic findings (Table 2), supported by the literature, with endocervical cells arranged in three-dimensional clusters and honeycomb sheets[7] with abundant vacuolar cytoplasm[4, 16]. In patients 3-4, moderate nuclear atypia with irregular nuclear membranes was seen[18], with either coarse chromatin and/or hyperchromatic nuclei and prominent nucleoli. Feathering or features suggestive of feathering[18] were also observed. Golden yellow intracytoplasmic mucin has been reported as a diagnostic clue for detecting GAS[5], and a yellow/brown mucinous hue was noted in one of our cases. On resection/surgical specimens, surface

atypia ranged from mild to moderate and was predominantly limited to areas overlying invasive tumor. Review of surface tumor cells in surgical specimens and correlation with cytologic samplings could be useful in making future recommendations for a cytologic diagnosis of GAS; however, further studies are needed.

In conclusion, GAS is a relatively uncommon aggressive tumor not related to HPV infection. As shown in our four patients, the initial findings on cervical cytology of GAS can vary, with GAS found in both patients with negative cervical cytology and those with AGC. Our study highlights the importance of noting a markedly increased number of bland-appearing endocervical cells on cervical cytology; in women without large ectropion, this finding should raise suspicion of GAS and warrants more careful review for nuclear atypia. This case series also highlights the utility of making a cell block from the residual liquid-based cytology material for further evaluation with immunohistochemical stains such as p16 and MUC6. Furthermore, a lack of yellow mucinous cytoplasm (reported as a specific indicator in previous case reports of GAS) does not exclude the possibility of GAS as it was present in only one of our four cases. Features such as numerous endocervical cells in three-dimensional clusters or honeycomb sheets with abundant vacuolated, foamy cytoplasm, mild to moderate nuclear atypia with irregular nuclear membranes, feathering, and a yellow/brown mucinous hue should raise the possibility of GAS and additional sampling can be suggested by the pathologist. Given the aggressive nature of GAS and the difficulties in initial diagnosis, increased awareness of this entity among pathologists is crucial.

Conflicts of Interest: The authors have no conflicts of interest. Dr. T. Darragh has been on advisory boards for Roche and BD.

Data Availability Statement: Research data are not shared.

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Patient	Age	Clinical presentation	Imaging findings	Gross features	Cytology diagnosis	Cervical biopsy/ECC and/or cone findings	Surgical diagnosis	IHC	Surgical Treatment	Chemo-therapy or radiation	AJCC stage; FIGO stage; Grade	Nodal or distant metastases	Follow up period (months) and Outcome
1	36	Incidental on TVH for AUB and adenomyosis	Adenomyoma and cystic change in LUS at the site of Cesarean section scar	Multiple small cysts filled with mucinous material in proximal endocervical canal	Negative	None (not performed)	Invasive GAS, margins negative, 2.2 cm, depth of invasion 0.8 out of 0.9 cm	p16- MUC6+	Total vaginal hysterectomy with right salpingectomy	No	pT1b1Nx; IB2, N/A.	None	17; alive and well
2	60	Post-coital bleeding	Multiple cysts in cervix with interval increase to 2.4 cm and myoma	N/A (hysterectomy not performed)	Negative	GAS	Invasive GAS, involving fallopian tube	p16- MUC6+ ER-	Aborted radical hysterectomy given positive lymph node on frozen section. pLND and salpingo-oophorectomy performed	Yes	N/A; N/A; not stated.	Obturator and supraclavicular lymph nodes; no other distant metastases	26; alive with disease
3	61	Abnormal pap with AGC	None	Two 0.4 thick walled cysts; cervix friable due to prior cone biopsy	AGC	GAS at least in situ	Invasive GAS, 4 cm, depth 0.8 cm, mainly in anterior cervix. LVI, margins negative	p16- MUC6+ ER-	Radical TAHBSO, pLND	Radiation given; no chemo-therapy	Not given; IB3; N/A.	None	29; alive and well
4	55	Abnormal pap with AGC	MRI: 1.3 cm heterogeneous enhancing lesion with cystic component	Bulbous cervix with 0.5 cm endocervical polyp	AGC	GAS at least in situ	Invasive GAS, 3 cm, margins negative, depth 0.5 cm	p16- ER- MUC6+ CEA+	Radical TAHBSO, pLND	No	pT1b1N0; IB2, well-diff.	None	14; alive and well

Table 1. Patient characteristics of four cases. AGC = atypical glandular cells. TVH = transvaginal hysterectomy. AUB = abnormal uterine bleeding. LUS = lower uterine segment. GAS = gastric-type endocervical adenocarcinoma. LVI = lymphovascular invasion. pLND = pelvic lymph node

dissection. TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy. IHC = immunohistochemistry. AJCC = American Joint Committee on Cancer. FIGO = International Federation of Gynecology and Obstetrics.

Patient	Endocervical cellularity	Architecture	Cell shape	Cytoplasm abundance	Cell borders	Nuclear outlines	Nuclear chromatin	Nucleoli number	Inflammation	Necrosis or apoptosis	Mitoses	Feathering
1	Moderate	Sheets and honeycomb	Cuboidal to columnar	Moderate, focal vacuoles	Well-defined	Smooth	Fine, no hyperchromasia	1-2 small	Moderate	None	None	None
2	Abundant	Single cells and honeycomb, picket fence, and 3D clusters.	Numerous tall columnar	Abundant, vacuolar and foamy with focal goblet cells	Well-defined	Smooth	Fine, vesicular nuclei	1-2 conspicuous	None	None	None	Present
3	Moderate	3D and honeycomb sheets	Columnar and polygonal	Abundant, vacuolar and foamy with brown-yellow hue	Ill-defined	Irregular, marked	Coarse, hyperchromatic	1-2 small, but prominent	None	Focal apoptosis, No necrosis	None	Present
4	Abundant	3D, picket fence clusters, few single cells	More polygonal than columnar	Moderate, focal vacuoles and goblet cells	Ill-defined	Irregular	Coarse	Prominent nucleoli	Abundant, suggestive of diathesis	None	Present	Suggestive of feathering

Table 2. Cervical cytology characteristics of GAS. 3D = three-dimensional.

Figure Legends:

Figure 1: A: Cervical cytology from Patient 1, with a few clusters of benign-appearing endocervical cells in the background of many squamous cells (Papanicolaou stain x400). B. On gross examination of the hysterectomy specimen from Patient 1, a 2 cm ill-defined, soft, tan lesion composed of multiple small cysts filled with mucinous material was identified in the superior (proximal) portion of the endocervical canal/lower uterine segment (cysts indicated with red arrows).

Figure 2. A. Cervical cytology from Patient 2, which consisted almost entirely of tall columnar endocervical cells with abundant vacuolar foamy cytoplasm, scattered goblet cells, and mild nuclear atypia with vesicular nuclei and conspicuous nucleoli (Papanicolaou stain x400). B. Endocervical cells with feathering (Papanicolaou stain x400).

Figure 3. A. Cervical biopsy from Patient 2 showed gastric-type endocervical adenocarcinoma (haematoxylin and eosin stain x100). B. MUC6 immunohistochemical staining on cervical biopsy from Patient 2 highlights the gastric-type endocervical adenocarcinoma (x200).

Figure 4. A: Left obturator lymph node from Patient 2, which showed metastatic gastric-type endocervical adenocarcinoma (haematoxylin and eosin stain x200). B and C: Fine needle aspiration biopsy of a left supraclavicular lymph node from Patient 2, which showed metastatic gastric-type endocervical adenocarcinoma (Papanicolaou stain x200 in B, x400 in C).

Figure 5. For patient 3: A. Three-dimensional cluster of endocervical cells with hyperchromatic nuclei and irregular nuclear membranes (Papanicolaou stain x400). B. Abundant vacuolar and foamy cytoplasm with yellow/brown hue to mucin (Papanicolaou stain x400). C. Markedly irregular nuclear membranes (Papanicolaou stain x400). D. Feathering (Papanicolaou stain x400). E. Cervical biopsy from Patient 3 with gastric-type endocervical adenocarcinoma (haematoxylin and eosin stain x200).

Figure 6. For patient 4, endocervical cells with (A) irregular nuclear membranes and prominent nucleoli (Papanicolaou stain x400), (B) nuclear atypia and mitosis (Papanicolaou stain x400), and (C) pseudostratified palisaded group of cells (Papanicolaou stain x400). D. Cell block from patient 4 with atypical glandular cells with vacuolar cytoplasm and occasional mitoses (haematoxylin and eosin stain x400). E. Negative p16 immunohistochemical stain on cell block from patient 4 (x400). F. Positive CEA immunohistochemical stain on cell block from patient 4 (x400).

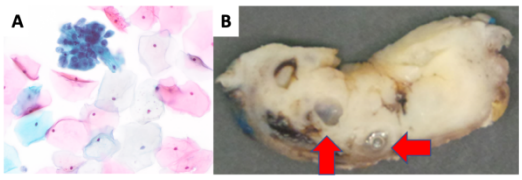
Patient	Age	Clinical presentation	Imaging findings	Gross features	Cytology diagnosis	Cervical biopsy/ECC and/or cone findings	Surgical diagnosis	IHC	Surgical Treatment	Chemo-therapy or radiation	AJCC stage; FIGO stage; Grade	Nodal or distant metastases	Follow up period (months) and Outcome
1	36	Incidental on TVH for AUB and adenomyosis	Adenomyoma and cystic change in LUS at the site of Cesarean section scar	Multiple small cysts filled with mucinous material in proximal endocervical canal	Negative	None (not performed)	Invasive GAS, margins negative, 2.2 cm, depth of invasion 0.8 out of 0.9 cm	p16-MUC6+	Total vaginal hysterectomy with right salpingectomy	No	pT1b1Nx; IB2; N/A.	None	17; alive and well
2	60	Post-coital bleeding	Multiple cysts in cervix with interval increase to 2.4 cm and myoma	N/A (hysterectomy not performed)	Negative	GAS	Invasive GAS, involving fallopian tube	p16-MUC6+ ER-	Aborted radical hysterectomy given positive lymph node on frozen section. pLND and salpingo-oophorectomy performed	Yes	N/A; N/A; not stated.	Obturator and supraclavicular lymph nodes; no other distant metastases	26; alive with disease
3	61	Abnormal pap with AGC	None	Two 0.4 thick walled cysts; cervix friable due to prior cone biopsy	AGC	GAS at least in situ	Invasive GAS, 4 cm, depth 0.8 cm, mainly in anterior	p16-MUC6+ ER-	Radical TAHBSO, pLND	Radiation given; no chemo-therapy	Not given; IB3; N/A.	None	29; alive and well

							cervix. LVI, margins negative						
4	55	Abnormal pap with AGC	MRI: 1.3 cm heterogeneous enhancing lesion with cystic component	Bulbous cervix with 0.5 cm endocervical polyp	AGC	GAS at least in situ	Invasive GAS, 3 cm, margins negative, depth 0.5 cm	p16- ER- MUC6+ CEA+	Radical TAHBSO, pLND	No	pT1b1N0; IB2; well-diff.	None	14; alive and well

Table 1. Patient characteristics. AGC = atypical glandular cells. TVH = transvaginal hysterectomy. AUB = abnormal uterine bleeding. LUS = lower uterine segment. GAS = gastric-type endocervical adenocarcinoma. LVI = lymphovascular invasion. pLND = pelvic lymph node dissection. TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Patient	Endocervical cellularity	Architecture	Cell shape	Cytoplasm abundance	Cell borders	Nuclear outlines	Nuclear chromatin	Nucleoli number	Inflammation	Necrosis or apoptosis	Mitoses	Feathering
1	Moderate	Sheets and honeycomb	Cuboidal to columnar	Moderate, focal vacuoles	Well-defined	Smooth	Fine, no hyperchromasia	1-2 small	Moderate	None	None	None
2	Abundant	Single cells and honeycomb, picket fence, and 3D clusters.	Numerous tall columnar	Abundant, vacuolar and foamy with focal goblet cells	Well-defined	Smooth	Fine, vesicular nuclei	1-2 conspicuous	None	None	None	Present
3	Moderate	3D and honeycomb sheets	Columnar and polygonal	Abundant, vacuolar and foamy with brown-yellow hue	Ill-defined	Irregular, marked	Coarse, hyperchromatic	1-2 small, but prominent	None	Focal apoptosis, No necrosis	None	Present
4	Abundant	3D, picket fence clusters, few single cells	More polygonal than columnar	Moderate, focal vacuoles and goblet cells	Ill-defined	Irregular	Coarse	Prominent nucleoli	Abundant, suggestive of diathesis	None	Present	Suggestive of feathering

Table 2. Cervical cytology characteristics of GAS. 3D = three-dimensional.



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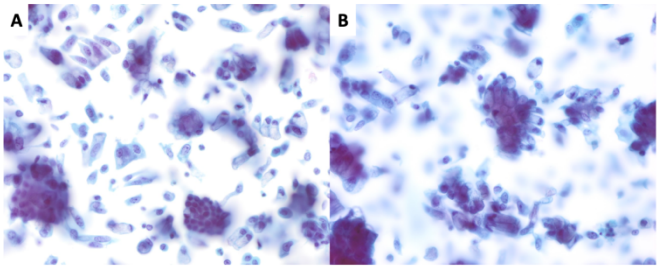

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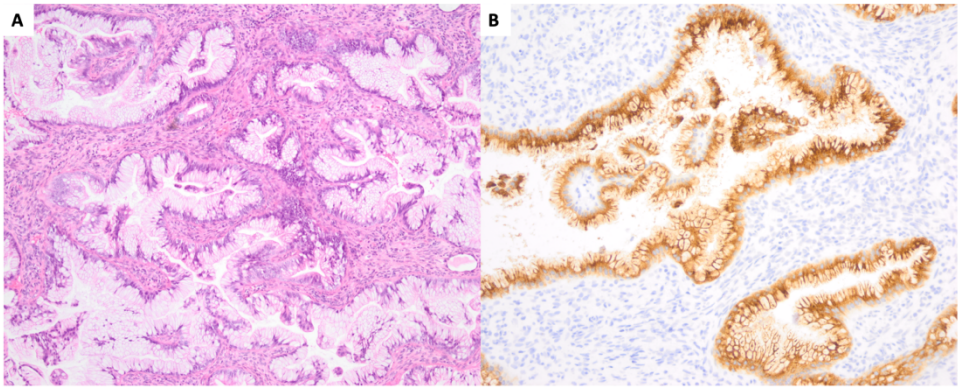

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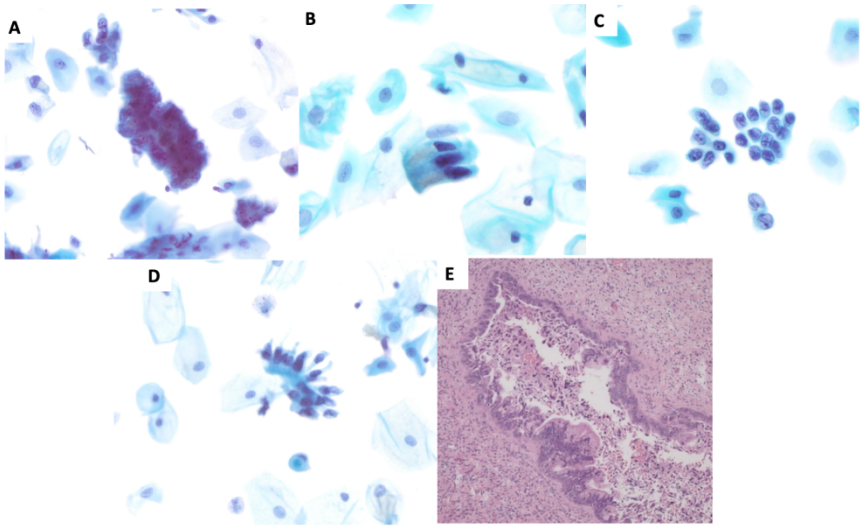

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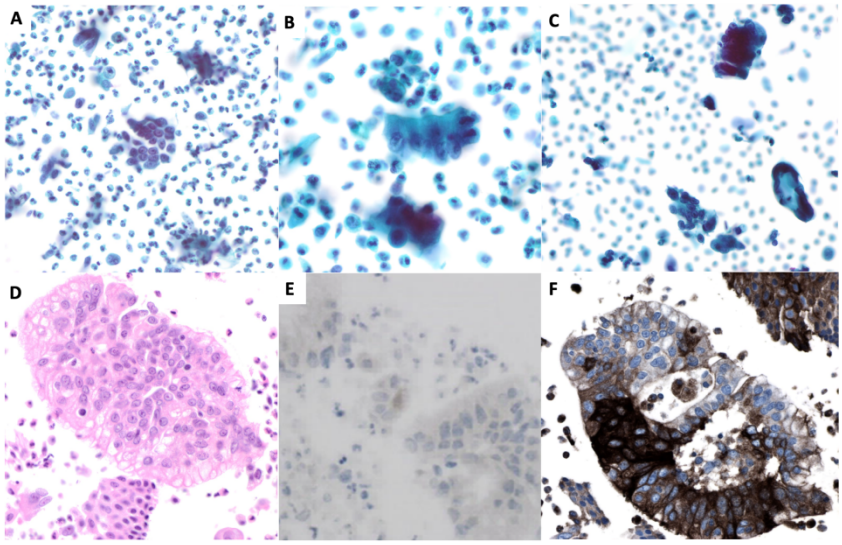

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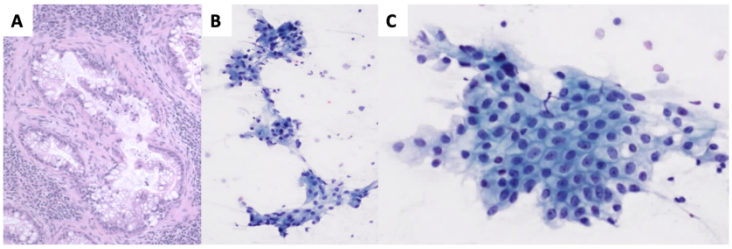

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