



## Gastric type adenocarcinoma of the cervix presenting as ovarian neoplasm

Jamie L. McDowell<sup>a,\*</sup>, Nicole Joseph<sup>b</sup>, Pallvi K. Singh<sup>a</sup>, Hong Yin<sup>b</sup>, Scott C. Purinton<sup>a</sup>

<sup>a</sup> Women's Health, 100 N Academy Ave, Geisinger Medical Center, Danville 17822, USA

<sup>b</sup> Laboratory Medicine, 100 N Academy Ave, Geisinger Medical Center, Danville 17822, USA

### ARTICLE INFO

#### Keywords:

Cervical cancer  
Gastric type  
Adenocarcinoma

### ABSTRACT

Gastric-type adenocarcinoma of the uterine cervix (GAS) is a rare subtype of mucinous adenocarcinoma, unrelated to HPV infection. It first appeared in the World Health Organization Classification of Tumours of Female Reproductive Organs in 2014.

This report discusses a 50-year-old, Caucasian female who presented with new onset abdominal pain, distension, and diffuse ascites. CT scan revealed an ovarian neoplasm later diagnosed as GAS on surgical pathology. Immunohistological stains were positive for PAX8, CK7, CK20 (focally strong), CAIX (strong), CEA (patchy), MUC6 (strong), HNF1b, UBC, RNA, KOC (focal), and P53 (wild type). Tumor cells were negative for p16, PAX2, ER, low-risk 5 HPV, high-risk 18 HPV, and CDX2. The proliferative index (Ki-67) was 20%. The patient is scheduled to receive systemic chemotherapy of cisplatin, paclitaxel, and bevacizumab. Following chemotherapy, she will undergo external beam radiation and vaginal brachytherapy.

The prevalence of GAS in the United States is currently unknown. Little is understood about the ideal treatment for this disease, and prognosis is very poor. As more cases are identified and reported, more targeted therapy be developed and trialed in these patients.

### 1. Introduction

Gastric-type adenocarcinoma of the uterine cervix (GAS) is a rare and aggressive type of cervical cancer that is unrelated to HPV infection. It was only recently reported in the literature, appearing for the first time in the World Health Organization (WHO) Classification of Tumours of Female Reproductive Organs in 2014. As a result of increased screening and prevention for HPV-related cervical cancer, the number of non-HPV related cervical cancers have also increased (Wilbur et al., 2014). It is important to recognize patients with this tumor as it is likely to be more aggressive. A study by Kojima A et al. in 2007 found the 5-year disease free survival was 30% compared with 74% in patients with usual type endocervical adenocarcinoma (UEA) (Kojima et al., 2007). This information has created a need for early detection methods and recognition of non-HPV related cervical tumors like GAS.

This report discusses a patient who presented with an ovarian neoplasm. Her final surgical pathology demonstrated gastric-type endocervical adenocarcinoma.

### 2. Case report

The patient was a 50-year-old, Caucasian female who presented to the emergency department with complaints of abdominal pain and distension for two weeks. Initially, the pain and bloating only occurred after meals, but on this day the discomfort was unprovoked. She also complained of constipation and decreased appetite, but denied weight changes or difficulty tolerating oral intake. She was followed regularly by her gynecologist for health maintenance and denied a history of abnormal pap smears. Her medical comorbidities included hypertension and a 30 pack-year smoking history.

Patient evaluation consisted of a physical exam, laboratory testing, and CT of the chest, abdomen and pelvis. Bimanual exam was significant for a large, mobile abdominal mass extending above the umbilicus, and obvious ascites with fluid wave. The uterus was palpated to be smooth and mobile, and no abnormalities were palpated in the vagina or cervix. Speculum exam was also unremarkable. Laboratory testing for tumor markers included CA-125 of 29.7 U/mL, CA 19-9 of <0.6 U/mL, and CEA of 1.1 ng/mL. The chest CT was negative for suspicious nodules or pleural effusion. The CT of abdomen and pelvis showed a large 12.9 × 18.9 × 13.3 cm left ovarian mass with diffuse, large volume ascites

\* Corresponding author.

E-mail address: [jmcdowell2@geisinger.edu](mailto:jmcdowell2@geisinger.edu) (J.L. McDowell).

<https://doi.org/10.1016/j.gore.2021.100888>

Received 3 August 2021; Received in revised form 3 November 2021; Accepted 6 November 2021

Available online 11 November 2021

2352-5789/© 2021 The Authors.

Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



**Fig. 1.** CT of the abdomen and pelvis demonstrating the pelvic mass and large ascites.

(Fig. 1). Hypodense lesions, presumed to be nabothian cysts, were noted in the cervical region. The patient was discharged home and paracentesis was performed the next day in the outpatient setting. Final cytology of the peritoneal fluid was negative for malignancy.

Following a discussion with the patient about the high likelihood of ovarian or peritoneal malignancy, she was taken to the operating room for an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of the pelvic mass.

Findings at the time of the surgery were as follows: a ruptured 25 cm left ovarian neoplasm, 5 L of mucinous ascites, grossly normal cervix, uterus, bilateral fallopian tubes and normal right ovary. There were no signs of extra ovarian disease, a normal appearing appendix and normal upper abdomen. The specimen was not sent for a frozen section. The surgery was uncomplicated and the patient was discharged home the following day after an uneventful post-operative course.

The histologic findings from the cervix revealed gastric-type endocervical adenocarcinoma. Small clusters of glands, deep to the overlying endocervical glands causing nearly no stromal response were identified (Fig. 2). A background of lobular, endocervical glandular hyperplasia was also observed. Morphological features of the tumor included glandular proliferation with tufting and infolding. The cells had voluminous, pale and eosinophilic cytoplasm with nuclear enlargement, hyperchromasia, loss of nuclear polarity, and admixed goblet cell differentiation. The ovarian mass revealed similar morphology and immunophenotype. Immunohistochemistry staining of both the primary and the metastasized tumor was positive for PAX8, CK7, CK20 (focally strong), CAIX (strong), CEA (patchy), MUC6 (strong), HNF1b, UBC, RNA, KOC (focal), P53 (wild type) and negative for p16, PAX2, ER, low-risk 5 HPV, high-risk 18 HPV, CDX2. The proliferative index (Ki-67) was 20%. The morphology of the GAS tumor metastasized to the ovary had features similar to a mucinous borderline tumor and could have been mistaken as a primary ovarian neoplasm rather than metastatic disease (Fig. 3).

The patient's clinical course and pathology were reviewed by

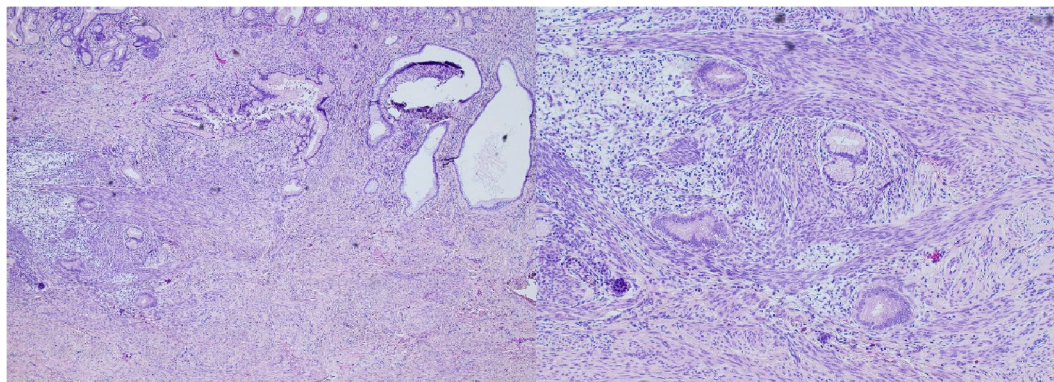
gynecologic oncology, radiation oncology, pathology, radiology, and hematology oncology at a multi-disciplinary tumor board conference. The patient was also discussed with specialists at two outside institutions, and the decision was made to proceed with systemic chemotherapy with cisplatin, paclitaxel, and bevacizumab. She will also receive external beam radiation therapy, followed by vaginal brachytherapy.

### 3. Discussion

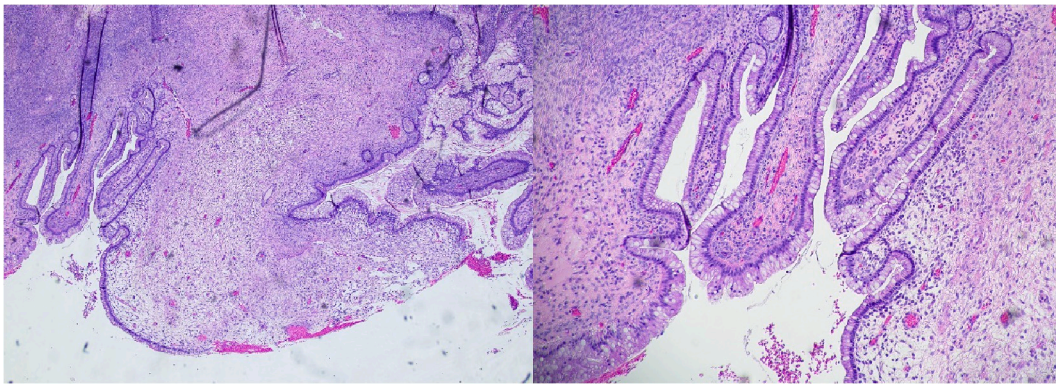
Cervical cancer is the second most common malignancy in females worldwide, with 20% of cases classified as adenocarcinoma (Nishio et al., 2019). It is estimated that 94% of cervical adenocarcinomas are HPV related, 90% of which are usual type endocervical adenocarcinoma (UEA). According to the 2014 WHO Classification, gastric type adenocarcinoma of the cervix is a subtype of mucinous adenocarcinoma and is not HPV related. Extremely well differentiated variants of GAS are called minimal deviation adenocarcinoma or adenoma malignum (Wilbur et al., 2014).

Several studies have demonstrated GAS as having a distinct immunohistochemical, morphologic, and clinical presentation when compared with other mucinous adenocarcinomas (Kojima et al., 2007; Nishio et al., 2019; Lu et al., 2019; Karamurzin et al., 2015). The morphologic criteria, described by Kojima A et al in 2007, include clear or pale eosinophilic cytoplasm, voluminous cytoplasm, and distinct cell borders (Park et al., 2011). Other features include glands that are simple; angulated, cystic and have areas of infolding or solid pattern. Glands can also be irregular, dilated and fused or have a cribriform pattern. Nuclear features include enlargement, hyperchromasia, and loss of polarity (Wilbur et al., 2014; Kojima et al., 2007; Lu et al., 2019). The characteristic HPV negative status can be confirmed with negative immunohistochemical staining for p16 (Park et al., 2011). In our case, negative p16, low-risk 5 HPV, and high-risk 18 HPV support that this tumor is not driven by HPV infection. Positive immunohistochemistry staining for CAIX and HNF1b are closely associated with this tumor type, and positive staining of mucin with MUC6 supports the mucinous differentiation (Park and Soslow, 2019). The gastric phenotype can be recognized with immunohistochemical stain HIK1083 and/or MUC-6 positivity, which react with gastric mucin (Kojima et al., 2007). Positive CEA staining helps to differentiate GAS from clear cell carcinoma (Park et al., 2011).

GAS is most prevalent in Japan, where it accounts for up to 25% of cervical adenocarcinomas (Wilbur et al., 2014). In the United States the true prevalence of this cancer is still unknown, as in the past it is likely to have been misdiagnosed as UEA, intestinal, or clear cell adenocarcinoma (Pirog, 2017). It is postulated that GAS may represent up to 20–25% of tumors previously classified as mucinous adenocarcinoma (Mikami and McCluggage, 2013). This is an important distinction, as GAS is



**Fig. 2.** Malignant endocervical glands deep within the stroma below the majority of endocervical glands, creating nearly no stromal response and demonstrating invasion (left 40× objective, right 100× objective).



**Fig. 3.** Glands within the ovary representing metastatic gastric-type adenocarcinoma (left 40× objective, right 100× objective) and resembling a primary ovarian neoplasm.

significantly more aggressive and carries a much poorer prognosis than that of mucinous adenocarcinoma (Nishio et al., 2019; Karamurzin et al., 2015). In 2019, a multi-institutional study identified predictors of poor outcome in GAS patients, including tumor diameter >40 mm, parametrial invasion, lymph node metastasis, poorly differentiated disease, and ovarian metastasis (Nishio et al., 2019). At least three of these features were seen in the patient reviewed in this case.

Our case is unique because the initial patient presentation suggested a primary ovarian neoplasm, which prompted primary surgical intervention rather than radiation with chemosensitization. However, the absence of an obvious cervical mass is not entirely uncommon for GAS due to its highly infiltrative growth pattern, and its usual location in the upper cervix (Kojima et al., 2018). Because GAS is so rare, there is a paucity of literature to guide treatment of the disease. In 2018, Kojima A et al performed a study that found GAS to be less chemosensitive than UEA when treated with docetaxel and carboplatin. They suggested the next step in developing an effective chemotherapy regimen for this cancer would be to focus on the development of specific molecular targeting therapy (Kojima et al., 2018).

In conclusion, gastric type adenocarcinoma of the cervix is a rare and aggressive form of non-HPV related cervical carcinoma. Atypical presentation of the disease is not uncommon. There is little information available to guide treatment for this disease, but hopefully as more cases are reported, more targeted chemotherapy regimens can be developed.

#### 4. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### *CRedit authorship contribution statement*

**Jamie L. McDowell:** Conceptualization, Writing – original draft.  
**Nicole Joseph:** Writing – original draft, Resources. **Pallvi K. Singh:**

Conceptualization, Review and editing. **Hong Yin:** Review and editing, Supervision. **Scott C. Purinton:** Review and editing, Supervision.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### References

- Karamurzin, Y.S., et al., 2015. Gastric-type endocervical Adenocarcinoma. *Am. J. Surg. Pathol.* 39 (11), 1449–1457.
- Kojima, A., et al., 2018. Chemosistance of Gastric-Type Mucinous Carcinoma of the Uterine Cervix: A Study of the Sankai Gynecology Study Group. *Int. J. Gynecol. Cancer* 28 (1), 99–106. <https://doi.org/10.1097/IGC.0000000000001145>.
- Kojima, A., Mikami, Y., Sudo, T., Yamaguchi, S., Kusanagi, Y., Ito, M., Nishimura, R., 2007. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am. J. Surg. Pathol.* 31 (5), 664–672.
- Lu, S., Shen, D., Zhao, Y., Kang, N., Wang, X., 2019. Primary endocervical gastric-type adenocarcinoma: a clinicopathologic and immunohistochemical analysis of 23 cases. *Diagn. Pathol.* 14 (1), 1–7.
- Mikami, Y., McCluggage, W.G., 2013. Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant, and malignant lesions. *Adv. Anat. Pathol.* 20 (4), 227–237.
- Nishio, S., et al., 2019. Analysis of gastric-type mucinous carcinoma of the uterine cervix—an aggressive tumor with a poor prognosis: A multi-institutional study. *Gynecol. Oncol.* 153 (1), 13–19.
- Park, K.J., et al., 2011. Unusual endocervical ADENOCARCINOMAS. *Am. J. Surg. Pathol.* 35 (5), 633–646.
- Park, K.J., Soslow, R.A., 2019. Neoplastic Lesions of the Cervix. (227–293). In: Nucci, M. R., Parra-Herran, C., Goldblum, J.R. (Eds.), *Gynecologic Pathology: A Volume in Foundations in Diagnostic Pathology Series*, second ed., vol. 8. Elsevier, pp. 227–293.
- Pirog, E.C., 2017. Cervical Adenocarcinoma: Diagnosis of Human Papillomavirus-Positive and Human Papillomavirus-Negative Tumors. *Arch. Pathol. Lab. Med.* 141 (12), 1653–1667.
- Wilbur, D.C., Mikami, Y., Colgan, T.J., Park, K.J., Ferenczy, A.S., Ronnett, B.M., Hirschowitz, L., Schneider, A., Loening, T., Soslow, R., McCluggage, W.G., Wells, M., Wright, T., 2014. Glandular tumors and precursors. In: Kurman, R.J., Carcangiu, M. L., Herrington, C.S., Young, R.H. (Eds.), *WHO Classification of Tumours of Female Reproductive Organs*. IARC Press, Lyon, pp. 183–189.