

A Case Study of Gastric Adenocarcinoma and Squamous Cell Carcinoma of the Cervix

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Abstract: Gastric adenocarcinoma (GAS) is a rare subtype of mucinous adenocarcinoma characterized by gastric differentiation and is unrelated to human papillomavirus (HPV) infection. This report discusses a 40-year-old female who presented with abdominal distension accompanied by increased abdominal circumference. CT of the abdomen and pelvis showed a large 21.0*12.7*26.0 cm mass later diagnosed as GAS combined with squamous cell carcinoma on surgical pathology. Immunohistological staining of GAS was positive for CK7, MUC6, PAX-8, CEA, and P53 (wild type) and negative for CDX2, CK20, ER, PR, P16, and WT1. The proliferative index (Ki-67) was 20%. Immunohistochemical staining of squamous cell carcinoma was positive for P16 and P53 (wild type), and the proliferative index (Ki-67) was 90%. However, the pathogenesis and molecular mechanisms of GAS have not been fully elucidated. As more cases are identified and reported, additional targeted therapies can be developed and tested in these patients.

Keywords: cervical cancer, gastric type, adenocarcinoma

Introduction

Cervical cancer is the third most common malignant cancer in women, with an incidence of approximately 570,000 new cases each year.¹ Although squamous cell carcinoma is the most common cervical cancer, the incidence of cervical adenocarcinoma has increased gradually in recent years, and it accounts for approximately 25% of all invasive cervical carcinomas.² Gastric-type adenocarcinoma (GAS) is a rare type of cervical adenocarcinoma and was defined as a subtype of mucinous adenocarcinoma with gastric differentiation in the 2014 World Health Organization (WHO) classification of cervical tumors.³ GAS has been reported to be aggressive and insensitive to chemical therapy and to have a poorer survival outcome than usual endocervical-type adenocarcinoma (UEA).^{4,5} Cervical squamous cell carcinomas and precancerous lesions are associated with high-risk human papilloma virus (HPV) infection. However, GAS is not related to HPV.^{2,6} The screening and early diagnosis methods for this disease are limited, the clinical stage of patients is late, and the 5-year survival rate is low. At present, there are no relevant studies on GAS complicated with cervical squamous cell carcinoma.

We report an interesting case in which a patient presented with an ovarian neoplasm but was diagnosed with gastric-type endocervical adenocarcinoma combined with cervical squamous cell carcinoma after surgical pathology.

Case Report

A 40-year-old woman with abdominal distension and increased abdominal girth presented at the hospital. She did not have massive vaginal secretions, postcoital bleeding, vaginal prolapse or other related symptoms.

A bimanual exam revealed a large abdominal mass extending above the umbilicus and massive ascites. The uterus was unclear, and no abnormalities were palpated in the vagina or cervix. The laboratory test results for tumor markers included carbohydrate antigen-199 (CA-199) >1000 U/mL, carbohydrate antigen-125 (CA-125) 176.6 U/mL and carcinoembryonic antigen (CEA) 20.06 ng/mL. The HPV16 subtype was positive, and no lesion cells were found via the ThinPrep cytologic test (TCT). CT of the abdomen and pelvis revealed a large 21.0*12.7*26.0 cm mass with diffuse, large-volume ascites (Figure 1).

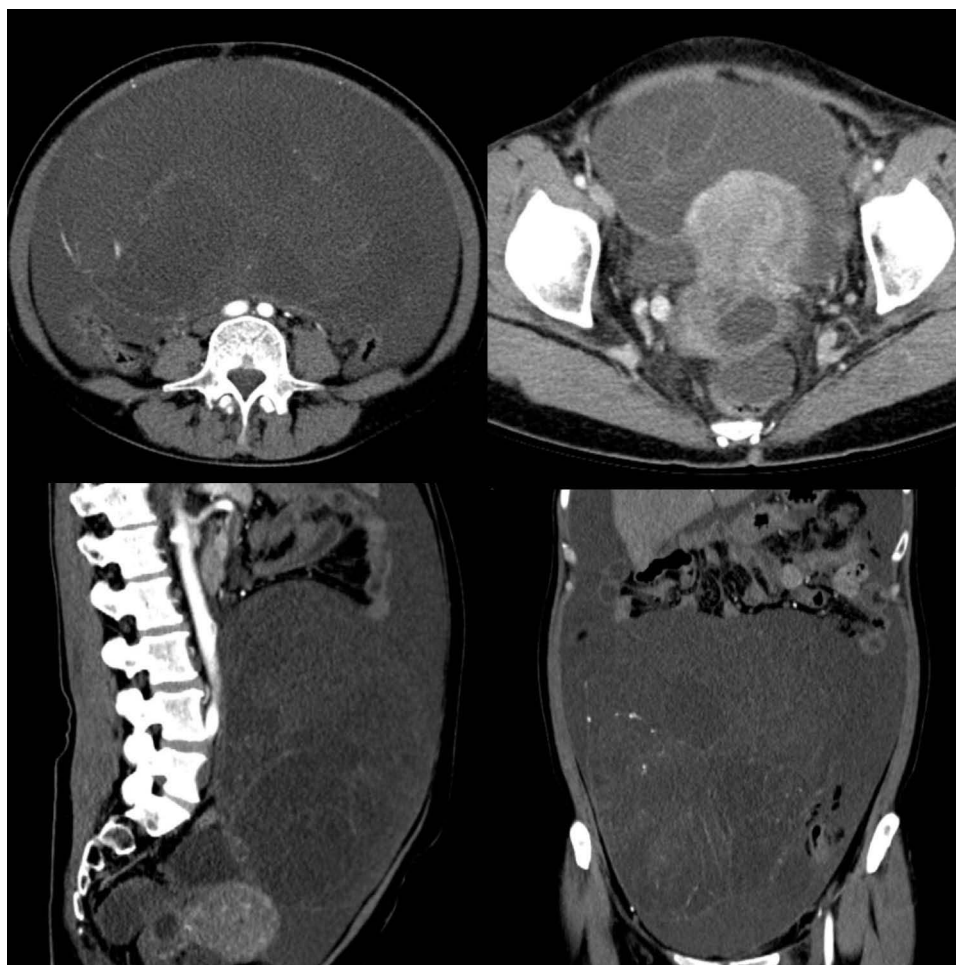


Figure 1 CT of the abdomen and pelvis demonstrating the pelvic mass and large ascites.

Hypodense lesions (3.1*2.1 cm), presumed to be nabothian cysts, were noted in the cervical region. The results of other examinations, including sigmoidoscopy and gastroscopy, were unremarkable. Abdominocentesis was performed, and cytology of the peritoneal fluid confirmed the presence of tumor cells. Therefore, she underwent exploratory laparotomy, total abdominal hysterectomy, bilateral tubo-ovariectomy, appendectomy and resection of the pelvic mass at our hospital.

The findings at the time of surgery were as follows: the pelvic cavity was filled with mucinous ascites and jelly like substances, and a 25 cm long right ovarian neoplasm was observed (Figure 2), a 10 cm long left ovarian neoplasm, a grossly normal cervix, and a uterus. Disease can be seen in the lateral peritoneum, bladder retraction peritoneum, rectum, colon, and uterorectum. The stomach and liver surface were normal, but no omentum was found. The specimens were subsequently sent for frozen sectioning of the suggested mucinous borderline tumor.

The histopathological result indicated a gastric-type mucinous carcinoma. The morphological features of the tumor included glandular proliferation with tufting and infolding. The cells had pale eosinophilic cytoplasm, voluminous cytoplasm with nuclear enlargement, hyperchromasia, and loss of nuclear polarity. The ovarian mass revealed similar morphology and immunophenotype. Immunohistochemical staining of both the primary and the metastasized tumor was positive for CK7, MUC6, PAX-8, CEA, and P53 (wild type) and negative for CDX2, CK20, ER, PR, p16, and WT1 (Figure 3). The proliferative index (Ki-67) was 20%. The morphology of the GAS tumor that metastasized to the ovary was similar to that of a mucinous borderline tumor and could have been mistakenly identified as a primary ovarian neoplasm rather than a metastatic disease.

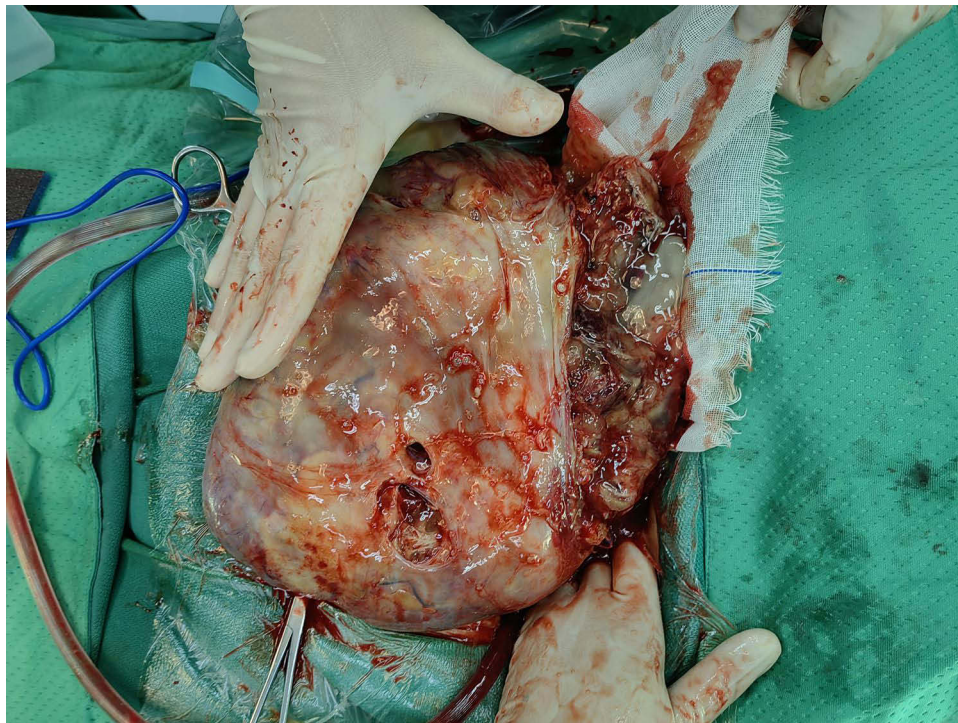


Figure 2 A ruptured 25 cm right ovarian neoplasm was found at the time of surgery.

In addition, a high-grade squamous intraepithelial lesion was found on the cervix. The focal area was a microinvasive squamous cell carcinoma with an invasion depth less than 3 mm. Immunohistochemical staining revealed P16 and P53 (wild type) positivity, and the proliferative index (Ki-67) was 90% (Figure 4).

A multidisciplinary tumor board conference included a discussion of gynecologic oncology, radiation oncology and pathology. Radiology was held to review the case, and chemotherapy and intraperitoneal thermoperfusion were recommended; however, the patient refused. The patient died four months after the operation.

Discussion

GAS is a unique tumor type with unique etiological, morphological and clinical features. Common clinical features include vaginal watery secretions, irregular abdominal pain, increased CA199, lesions located high in the endocervical canal, and invasion of peripheral and distant organs; moreover, the appearance of the cervix can often be characterized by no obvious clinical abnormalities or spherical enlargement. A unique clinical aspect of GAS is the potential presence of metastases to the ovaries, peritoneal surface, and intraabdominal organs.⁵ In this study, ovarian metastases were observed.

The diagnosis of GAS mainly depends on histopathology, combination of cytology and MRI.⁶ The morphologic criteria of GAS include clear or pale eosinophilic cytoplasm, voluminous cytoplasm, and well-defined cell borders.^{7,8} GAS typically presents a gastric mucin phenotype that is immunopositive to mucin MUC6, cytokeratin 7 (CK7) and HIK1083, with estrogen receptor (ER), progesterone receptor (PR) and P16 immunostaining often negative, P53 staining is mutant.⁶ 75% of cases were positive for carcinoembryonic antigen(CEA) and half were positive for CK20 staining.⁸ Imaging findings in cervical squamous cell carcinoma (SCC) include hypoechoic signals, while cervical adenocarcinoma is isoechoic. The imaging presentation of GAS is usually a predominantly solid tumor with or without a mixed cystic component.⁹ A significant increase in the number of cervical cells on cervical cytology should raise suspicion of GAS and lead to closer scrutiny of nuclear atypia.⁷

The 5-year disease-free survival rate in patients with GAS was 30%, whereas it was 74–77% in patients with UEA.⁶ GAS is more likely to recur than other types of cervical adenocarcinoma.⁴ The prognostic factors for GAS include

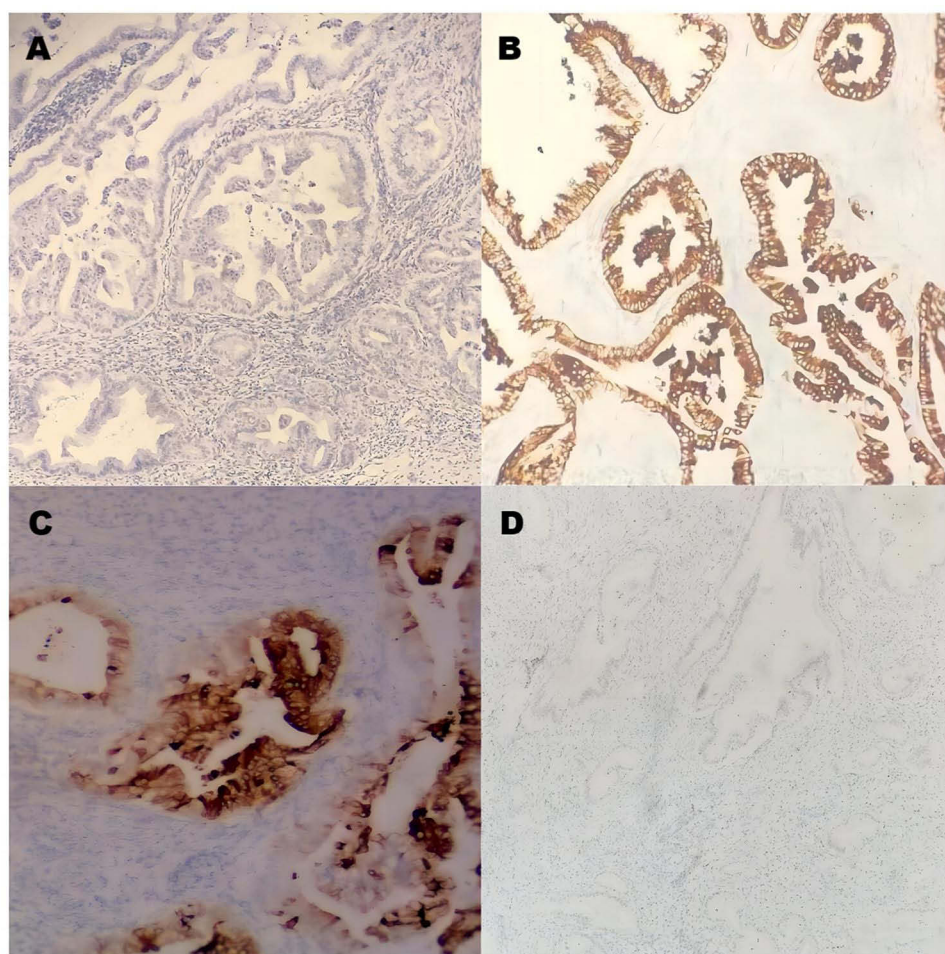


Figure 3 Immunohistochemical staining of GAS. Histologic ((A) hematoxylin and eosin staining) and immunohistochemical (B–D) findings. (A) The tumor shows gastric-type differentiation with abundant clear or pale, eosinophilic cytoplasm with atypical nuclei. (B and C) Immunohistochemical staining for MUC6 and CEA was positive. (D) P53, wild type.

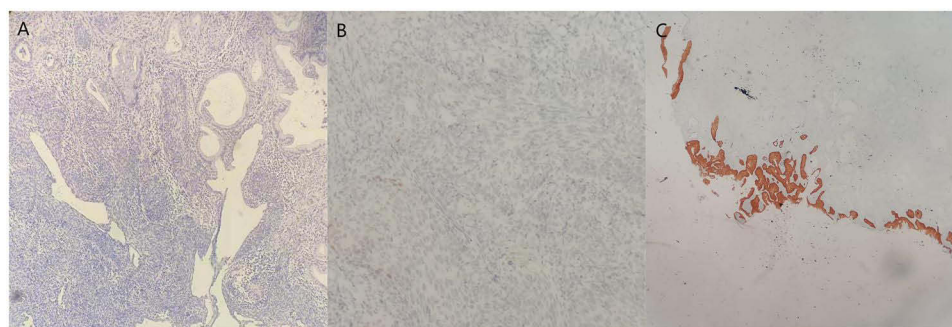


Figure 4 Immunohistochemical staining of squamous cell carcinoma (A) A high-grade squamous intraepithelial lesion and microinvasive squamous cell carcinoma were found on the cervix. (B) P53 was the wild type. (C) Immunohistochemical staining was positive for P16 in squamous cell carcinoma and negative in GAS.

a tumor diameter > 4 cm, paracentral infiltration, lymphatic metastasis, poorly differentiated carcinoma and ovarian metastasis. The poor prognosis may be due to difficulties in early detection and resistance to chemotherapy and radiotherapy.⁴

GAS is currently treated in the same way as other types of cervical cancer, and surgical resection is a strong treatment option for GAS. Patients in advanced stages require chemoradiotherapy and radiotherapy. Nishio's study demonstrated

that there was less radio-sensitivity in patients with GAS than in patients with UEA (50% vs 81.8%, respectively; $P < 0.001$).⁴ Chemotherapy with carboplatin and docetaxel is also less effective for GAS than for UEA.¹⁰ Therefore, there is an urgent need for research and development of targeted therapy for GAS to improve patient outcomes.

Several scholars have analyzed the phenotypic characteristics of HPV-associated gastric cervical adenocarcinoma and found that TP53, CDKN2A, KRAS, STK11, ATM and NTRK3 mutations were more common in gastric adenocarcinoma^{5,11,12}. STK11 mutation was associated with poor survival in GAS patients, which will promote genomic profile-guided targeted therapy for precision oncology in GAS patients¹³. A previous study revealed both NTRK1 and NTRK3 mutations in GAS, and the tropomyosin receptor kinase (TRK) inhibitor larotrectinib has been approved for the treatment of solid tumors with NTRK-related mutations and integrations.¹¹ Approximately 5–15% of GASs are HER2-amplified, and patients with ERBB2 alterations treated with the anti-HER2 antibody trastuzumab have excellent clinical outcomes.⁵ In terms of novel agents, genome-wide analysis using next-generation sequencing (NGS) has identified several new molecular targets. However, there are few data on the efficacy and treatment of gastric adenocarcinoma based on sequencing results. Larger prospective studies are warranted to assess whether the presence of specific genetic alterations is associated with outcome in patients with GAS.

Conclusion

GEA is a rare histologic subtype of cervical adenocarcinoma that is not secondary to HPV infection, is usually diagnosed at late stages and generally has poor outcomes. This is likely due to tumor biology in addition to poor detection via traditional screening methods. The management approach for GEA should include surgery, chemotherapy, radiation therapy, immunotherapy and even targeted therapy. Finally, a cancer registry of these rare tumors may aid in the development of more robust practice guidelines.

Ethics Committee

The study protocol was approved to carry out by the Ethics Committee of Yantai Affiliated Hospital of Binzhou Medical University, and institutional approval was not required to publish the case details. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The study was performed in accordance with the principles of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest related to this work.

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