Pathological features of gastric-type endocervical adenocarcinoma: A report of two cases

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Abstract. Gastric-type endocervical adenocarcinoma (GEA) is an uncommon form of uterine cervical adenocarcinoma with an unfavorable prognosis. The tumor consists of glands exhibiting a morphological resemblance to gastric cells and occasionally manifests features akin to pancreaticobiliary mucinous adenocarcinoma. GEA differs from the typical cervical cancer, particularly in its lack of association with the human papillomavirus. Immunophenotypic analysis suggests intestinal differentiation. The present study reports two cases of GEA occurring in postmenopausal individuals who were diagnosed in Lishui Central Hospital (Lishui, China) between January 2015 and January 2023. Microscopic examination revealed cysts lined with mucinous cells within the tumors. Immunohistochemical assays confirmed the positivity of the tumors for cytokeratin 7, mucin (MUC)5AC, and mutant tumor protein p53, while the results were negative for tumor suppressor p16, and in one case for paired box protein 8, consistent with characteristics of mucinous adenocarcinoma originating from the gastrointestinal tract. Programmed death-ligand 1 expression was also negative. The proto-oncogene K-ras was identified using amplification refractory mutation system polymerase chain reaction. Both cases were negative for mutations in codons 12 and 13 of exon 2, codon 61 of exon 3 and codon 146 of exon 4, but were positive for wild-type K-ras. Clinical follow-up revealed a potential association between histopathological features and resistance to chemotherapeutic drugs. The infrequency of this tumor type may contribute to diagnostic challenges.

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Introduction

Malignancies in the uterine cervix arise from the epithelial lining, resulting in squamous carcinoma and adenocarcinoma (1,2). Cervical cancer, predominantly of squamous epithelial origin, is linked to high-risk human papillomavirus (HPV) infection. The high incidence of squamous cell cervical carcinoma is attributed to HPV, offering an opportunity for global eradication through HPV vaccination (3). HPV tests, including HPV DNA and thin-prep cytology test (TCT) screening, aid in the early detection of cervical squamous epithelial lesions. With the implementation of the HPV vaccine, cervical squamous cancer rates have been decreasing. The PATRICIA trial, suggested that following the use of the bivalent anti-type 16 and 18 HPV vaccine in ~9,000 vaccinated women aged 15-25 years, high-grade cervical intraepithelial neoplasia ($CIN2^+$/$CIN3^+$) incidence was reduced compared with that in controls. Also cross-protection against persistent infection was found with the non-vaccine oncogenic HPV types 31, 33 and 45 at ~3 years after complete vaccination. $CIN2^+$ associated with HPV-16/18 was reduced by 93% and $CIN2^+$ associated with HPV-31/33/45/52/58 was reduced by 53% (4,5).

According to the 2020 World Health Organization Classification (4), cervical adenocarcinomas form a spectrum from well-differentiated adenoma malignum (mucinous variant of minimal deviation adenocarcinoma) to poorly differentiated, invasive gastric-type adenocarcinoma (6,7). The gastric type cervical cancer encountered in the present study is often overlooked due to its rarity. Notably, endocervical carcinoma, specifically gastric-type cervical adenocarcinoma, is unrelated to HPV infection. Gastric-type adenocarcinomas (GASs) constitute a heterogeneous group of tumors with varying morphological features, presenting challenges in diagnosis (8). Between January 2015 and January 2023, two cases of gastric endocervical adenocarcinoma were diagnosed and the patients were admitted to Lishui Central Hospital (Lishui, China). The present study describes the pathological findings and

immunostaining of relevant markers, providing a comparison with previously published data. The profile contributes insights for future diagnoses and aims to improve the understanding the underlying mechanisms of tumor genesis.

Immunohistochemically, clinical specimens in the present study were tested for mucinous adenocarcinoma biomarkers, along with the mutant forms of tumor suppressor genes tumor protein p53 (p53) and p16. The K-ras proto-oncogene, frequently mutated in tumors of various histological origins (9,10), was assessed using an enriched polymerase chain reaction (PCR) method for point mutation tests and restriction fragment length polymorphism, amplification refractory mutation system (ARMS). This method measured K-ras genotypes, providing data to screen parameters for diagnosis and predict clinical outcomes in the rare gastric-type endocervical adenocarcinoma (GEA) tumor.

Case report

Case presentation. Between January 2015 and January 2023, two cases of GEA were diagnosed at Lishui Central Hospital. The general information of the two patients is summarized in Table I.

Case 1. A 52-year-old woman observed an increase in vaginal discharge, which was watery and white, in January 2015. There was no itching in the external genital area, but discomfort was felt in the lower abdomen. A pelvic computed tomography (CT) scan showed a markedly enlarged cervix, with a cystic solid mass measuring ~5.4x4.1x7.6 cm. The boundaries of the mass were unclear, and the contrast-enhanced scan displayed uneven enhancement. The possibility of cervical malignancy could not be ruled out. TCT results were negative, while tumor markers indicated elevated cancer antigen (CA)125 levels at 497.3 U/ml (normal range, 0-35 U/ml) and CA19-9 levels at 2,339.4 U/ml (normal range, 0-37 U/ml). A high-risk HPV test using the Hybrid Capture 2 assay (HC2; Digene; Qiagen, Inc.) was also negative. After admission to the hospital, the patient underwent a radical removal of the uterus and bilateral adnexa, with pelvic cavity cleaning.

Upon histological examination, at low magnification, the tumor appeared to consist of dilated cysts or glands with stromal infiltration. These cysts were lined by a single- or multi-layered mucinous epithelium. At high magnification, the cells showed varying degrees of atypia, with clear or pale cytoplasm, vesicular nuclei and prominent nucleoli. The cells exhibited distinct borders. Immunohistochemical markers play a crucial role in determining the molecular characteristics and behavior of tumors. In this case, positive expression of cytokeratin (CK)7, mucin (MUC)5AC, and p53 suggested specific features of the tumor; in cervical HPV-associated adenocarcinoma, p53 is expressed in its wild-type form, while in cervical gastric-type adenocarcinoma, p53 is expressed as a mutant variant. While negative results for estrogen receptor (ER), progesterone receptor (PR) and paired box protein 8 (PAX8) indicated the absence of markers associated with other types of tumors or conditions.

The final pathological diagnosis indicated nodular moderate- to poorly differentiated adenocarcinoma of the gastric type, infiltrating all layers of the cervical wall without breach of the serosa. Observations noted cancer thrombi within blood vessels and nerve involvement.

In July 2021, the patient commenced radiotherapy using a pelvic intensity-modulated radiation therapy field covering both the primary focus and pelvic lymphatic drainage area. The treatment involved the following parameters: 6 MV X-rays; source-axis distance, 100 cm; 95% planning target volume, 50 Gy/25 fractions, 5 fractions/week; cisplatin, 79 mg/week administered over five cycles with a cycle per week. Subsequently, the patient underwent chemotherapy at ~1-month intervals in August, September and October 2021. The chemotherapy regimen included 500 mg albumin-bound paclitaxel (day 1) and 48 mg cisplatin (days 1-3), with one cycle being 3 weeks.

The patient was readmitted to the hospital in March 2022, with symptoms of abdominal distension, abdominal pain and cessation of gas passage for 1 day. An emergency abdominal CT scan revealed post-cervical cancer surgery changes, such as thickening and exudate in the presacral soft tissues and perirectal fascia, along with widespread thickening of the omentum and fascia. These findings raised concerns about the possibility of metastasis. The patient who was alive with disease ultimately declined further radiation and chemotherapy, and follow-up revealed that the patient is currently self-administering traditional Chinese medicine.

Case 2. A 47-year-old woman presented to Lishui Central Hospital in March 2021 with the chief complaint of persistent vaginal bleeding for 2 months. An ultrasound examination revealed a low echogenic mass measuring 61x41x39 mm in the posterior wall of the cervix, with unclear borders. Pelvic magnetic resonance imaging revealed irregular cervical thickening and multiple internal cystic lesions, some with separations. Tumor marker levels indicated potential cervical malignancy, with CA125 at 497.30 U/ml and CA19-9 at 2,339.40 U/ml. The patient underwent a radical removal of the uterus and bilateral adnexa with pelvic cavity cleaning.

Microscopic examination revealed a tumor consisting of variable-sized cysts with diverse architectures, ranging from well-differentiated dilated glands lined by mucinous epithelium to a cribriform pattern. At high magnification, tumor cells displayed pale cytoplasm and cytologic atypia, varying from mild to severe. Lymphovascular invasion was observed, indicating the presence of tumor cells within lymphatic or blood vessels, which is an important prognostic factor for tumor spread and metastasis. Immunohistochemical analysis showed negative results for ER, PR, and p16, indicating their absence in the tumor cells. Positive staining was observed for MUC5AC, p53, PAX8 and CK7.

Following surgery, the patient underwent whole pelvic intensity-modulated radiotherapy of 48 Gy/24 fractions starting in July 2021, with subsequent sessions 11 days later and then at ~1-month intervals in August, September and October 2021. After ruling out contraindications, the patient received intravenous chemotherapy with 400 mg albumin-bound paclitaxel and 500 mg carboplatin for 3 weeks. However, recurrence occurred 1 year later. During a telephone follow-up, it was learnt that the patient who was alive with disease is currently considering whether to enroll in a clinical trial.

Table I. General information on the cases entering the study.

Case no.	Sex	Age, years	Clinical findings	HPV
1	Female	52	Watery vaginal discharge	Negative
2	Female	47	Vaginal bleeding	Negative

HPV, human papillomavirus.

Methods. An analysis was conducted on cases of GEA a rare tumor encountered at Lishui Central Hospital, with only two cases identified over an 8-year period.

Pathological findings. It is noteworthy that both patients were in the menopausal age group, distinguishing them from the more common squamous cell carcinoma (SCC) observed in younger individuals. The diagnosis of adenocarcinoma, supported by the presence of cysts lined with mucinous epithelium and glands with stromal infiltration, was confirmed as GEA through the immunohistochemical data. In case 1, GEA was diagnosed based on clinical and histopathological examination of the lesion obtained from hysterectomy specimens. Aggressive tumor behavior, characterized by perineural invasion and intravascular thrombus, was observed. In case 2, in addition to the morphological features of cervical adenocarcinoma, lymphovascular invasion was identified in the tumor.

Microscopic observation. Microscopically, the tumor was composed of cysts of variable sizes with diverse architectures, from well-differentiated dilated glands linked by mucinous epithelium to a cribriform pattern. At low magnification, the tumor was comprised of dilated cysts or glands with stromal infiltration, lined by a single- or multi-layered mucinous epithelium (Fig. 1A). At high magnification, tumor cells were observed to show pale cytoplasm and cytologic atypia with mild or severe degrees. The morphological appearances of the tumor cells differed from usual HPV-related cervical adenocarcinomas, as apical mitotic figures and apoptotic bodies were not always present (Fig. 1B). The clinical details are presented in Table I, and the representative histopathological findings of the patients are depicted in Fig. 1. Cervical surgical specimens for analysis were retrieved from the archival specimen registry at the Department of Pathology, Lishui Central Hospital, and microsections of 2 mm were prepared using a Leica machine (RM2245; Leica Microsystems, Inc.) and mounted on clean glass slides. Sections were fixed with 4% paraformaldehyde and stained with hematoxylin and eosin (H&E) at room temperature for 1 h, before review under a microscope (BX40-72H02; Olympus Corporation).

Immunohistochemical staining. Table II outlines the markers to be detected and the sources of the commercial antibodies employed in this study. Immunohistochemical staining was conducted according to a previously described method (10,11), with slight modifications. Microsections were dewaxed, and antigenic epitopes were decrosslinked by heating at 95˚ for 5 min. After drying, the sections were co-incubated with primary antibodies, diluted at a ratio of 1:100, at room temperature overnight. Subsequently, these were conjugated with labeled secondary antibodies and developed using a DAB kit. Tumor suppressor p53 staining that was entirely negative or strongly and diffusely positive (with a proportion of tumor cell nuclei >80%) was considered mutation-type. By contrast, heterogeneous staining of p53 was considered wild-type (11,12). Histological markers CK7 and MUC5AC were assessed and showed cytoplasmic staining. For p16, diffuse cytoplasmic staining was considered positive, while corresponding focal or patch staining was deemed negative. Despite HIK1083 being considered as an immunohistochemical marker of gastric-type differentiation (13), it was not utilized in this study due to limitations in departmental funding and resources.

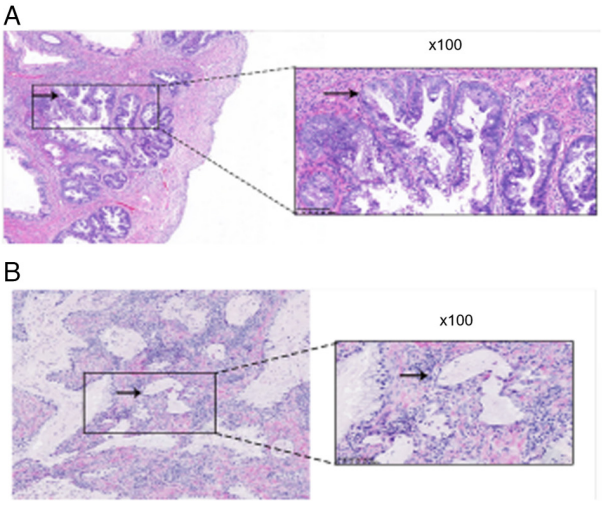

Figure 1. Representative microscopic views of the lesions in the two patients with gastric-type endocervical adenocarcinoma. (A) In case 1, the glands in the tumor exhibited slight irregularities, with enlarged nuclei in the tumor cells, accompanied by visible nucleoli. The cytoplasm of the cells was abundant with the existence of acidophilia (eosinophilia) and transparent regions. (B) In case 2, the nuclei of the tumor cells were enlarged, with an increased nuclear-to-cytoplasmic ratio. The enlarged nuclei were composed of prominent nucleoli. The morphology in the cytoplasm appeared similar to (A). Scale bar, 20 μm.

Detection of mutant proto-oncogene K-ras with ARMS-based PCR

Primer design and ARMS PCR protocol. The sequences of the ARMS primers used for the mutation detection are as previously described (9). Each PCR utilized one ARMS primer and a common reverse primer for mutation detection.

PCR amplification. The test was conducted as previously reported (14), with some modifications. For each reaction, 5 μl of a supernatant containing genomic DNA as a template was added to a final volume of 50 μl. This volume included 1 μl of a 25 pmol reverse primer, 1 μl of a 12.5 pmol control forward primer, 1 μl of a 25 pmol control reverse primer, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.2 mM $MgCl_2$, 200 μM deoxynucleoside triphosphates and 2 units of Taq DNA polymerase. The reaction was performed in a DNA Thermolyne (Thermo Fisher Scientific, Inc.) with the following program: Initial denaturation at 95˚C for 5 min, followed by 25 cycles of denaturation at 95˚C for 25 sec, annealing at 64˚C for 20 sec and elongation at 72˚C for 20 sec. Subsequently, 30 cycles were

Table II. Source of the primary antibodies, and the immunostaining patterns of the immunohistochemical markers.

Markers detected	Localization (reactivity)	Source of primary antibody
CK7	Cytoplasmic staining (+)	Fuzhou Maixin Biotech, Co., Ltd.
MUC5AC	Cytoplasmic staining (+)	Fuzhou Maixin Biotech, Co., Ltd.
p53	Nuclear staining (+)	Fuzhou Maixin Biotech, Co., Ltd.
PAX8	Nuclear staining (+)[a]	Origene Technologies
p16	Nuclear/cytoplasm staining (-)	Yichen Biotechnology, Ltd.
ER	Nuclear staining (-)	Roche Diagnostics (Shanghai), Ltd.
PR	Nuclear staining (-)	Yichen Biotechnology, Ltd.
PD-L1	Membrane staining (-)	Amoy Diagnostics, Co., Ltd.

[a]Only for case 2. Positivity of <50% of cells viewed was regarded as negative. CK, cytokeratin; PAX8, paired box 8; p53, tumor protein p53; ER, estrogen receptor; PR, progesterone receptor; MUC, mucin; PD-L1, programmed death-ligand 1.

performed with denaturation at 95˚C for 25 sec, annealing at 64˚C for 30 sec and elongation at 72˚C for 20 sec. The signals of fluorescence dyes 6-carboxyfluorescein and hexachloro-fluorescein. No signals were registered when the system cooled to 60˚C. The amount of amplified product was plotted against time to obtain a real-time curve. The amplification products were verified by loading on a 0.8% agarose gel for electrophoresis.

Results. Only two cases of GEA were identified in the Lishui Central Hospital over an 8-year period from January 2015 to January 2023, aligning with the low incidence of this tumor type. Notably, both patients were in the menopausal age group, unlike the more common SCC observed in younger individuals.

Immunohistochemistry. Relevant markers associated with carcinogenesis were detected immunohistochemically, the data and the immunostaining pattern are detailed in Table II. The results were classified as negative, focally positive (<50% cell staining) or diffusely positive (≥50% cell staining). In both patients, common findings included several markers being diffusely or focally positive, such as CK7, MUC5AC and mutant tumor suppressor p53 (Fig. 2). Negative markers included ER, PR, and PAX8. Programmed death-ligand 1 (PD-L1) testing was conducted, and the tests yielded negative results. In case 2, negative results were found for the ER, PR, p16 and PD-L1 immunohistochemical markers, while positive expression was found for CK7, MUC5AC, PAX8, and mutant p53. The data suggested an epithelial origin and a mucinous cell phenotype.

Positive staining for mutant p53 encoding protein using a specific antibody indicated abnormal expression (Fig. 3). Dysregulation or mutations in the p53 gene can lead to loss of its tumor suppressor function, contributing to tumor development and progression (15,16).

ARMS-based PCR. The analysis of K-ras oncogene mutations in the two GEA patients, as indicated by the slope shape curve for wild-type K-ras and the plateau shape for mutant K-ras, suggested that K-ras was of the wild type. No mutations in codon 12 and 13 of exon 2, codon 61 of exon 3 and codon 146 of exon 4 were observed (Fig. 3).

Discussion

In the present study, two cases of GEA were examined. This tumor type is distinguished from common adenocarcinoma of the uterine cervix in terms of etiology, biological behavior and clinical outcome. Morphologically, the tumor is comprised of numerous glands, varying from well to poorly formed. Eosinophilic or clear cytoplasm, foamy cytoplasm, vesicular nuclei and prominent nucleoli characterize the tumor cells (17).

It has been postulated that lobular endocervical glandular hyperplasia may serve as a precursor to gastric lesions in GEA. Minimal deviation adenocarcinoma is considered an extremely well-differentiated form of gastric-type adenocarcinoma. Compared with common cervical adenocarcinomas, gastric-type adenocarcinoma is associated with a poorer prognosis (18). By raising awareness of precursor and well-differentiated forms of GEA, an earlier diagnosis could potentially be facilitated by pathologists, leading to prompt treatment and improved patient outcomes.

In the present study, the two patients with GEA both experienced an unfavorable clinical outcome, as observed after diagnosis. The clinical manifestations and the pathological findings were resembling, as per immunohistochemical findings, the profile was similar except that PAX8 was positive in case 2 (18); this may reflect a variation in histological differentiation, but was not related to their prognosis. Both patients had signs of tumor expansion, notably in case 2, where lymphovascular invasion was observed. The two patients underwent radical removal of the uterine cervix and surrounding tissues, and were administered radio- and chemotherapy afterwards. The patient in case 1 was readmitted after the first round of therapy. Both patients manifested a poor prognosis as suggested by signs of metastasis and recurrence.

GEA is not associated with HPV. The etiology may indicate differences in the genesis mechanism. A notable alteration in known cancer-related genes, as revealed by the present study, is the mutation of the tumor suppressor p53. This mutation is rare in other types of cervical cancer, including both SCC and adenocarcinoma of the cervix (7,19). The oncogenic products encoded by HPV were not detected in the present cases, which is commonly observed in the same type of cancer, i.e. adenocarinoma of other histological

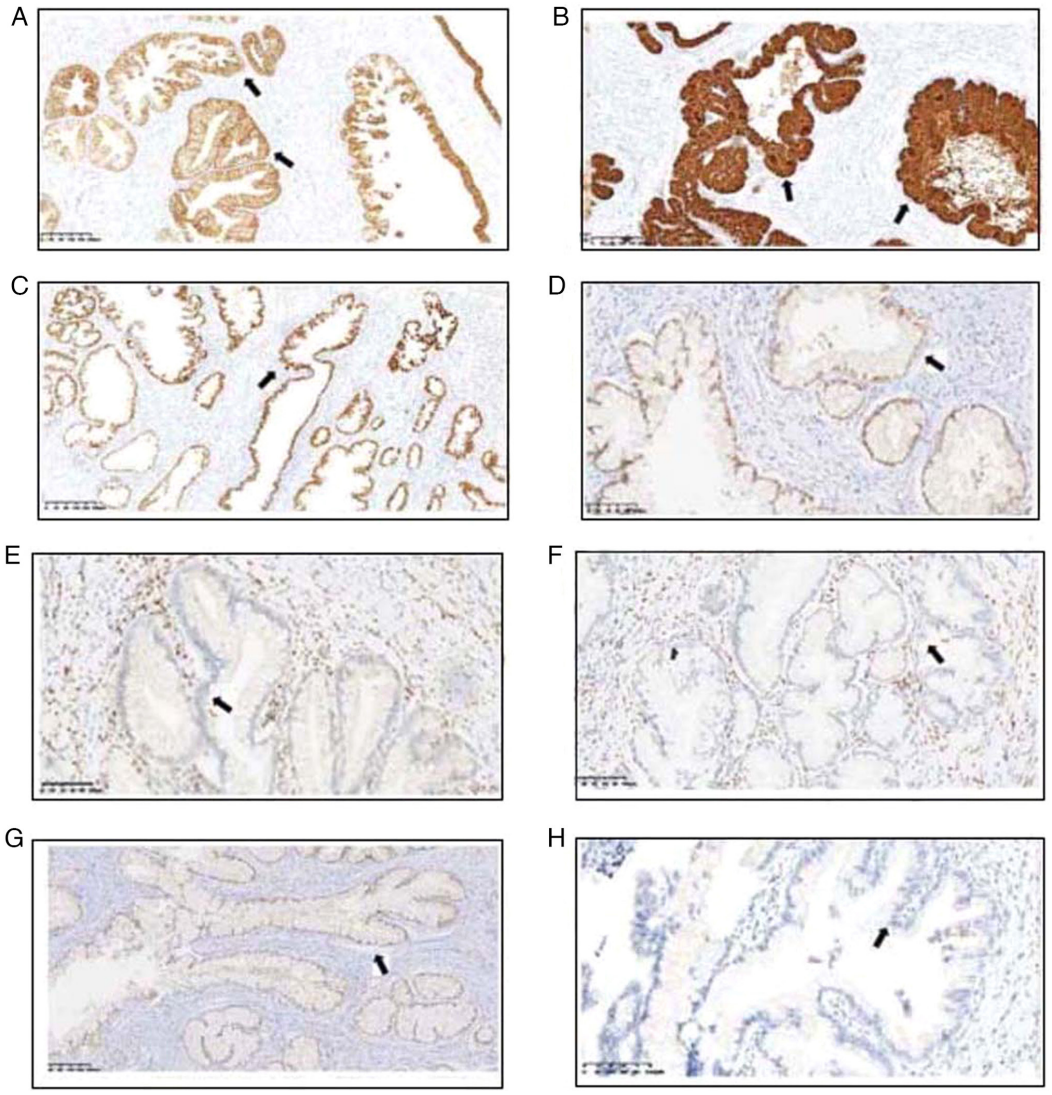

Figure 2. Immunohistochemical staining of histological markers and two tumor suppressive gene products. (A) Cytoplasmic diffusely positive result for cytokeratin 7; (B) cytoplasmic diffusely positive result for mucin 5AC; (C) nuclear diffusely positive result for mutant tumor protein p53; (D) nuclear staining positive for paired box protein 8; (E) negative result for tumor protein p16; (F) negative result for estrogen receptor; (G) negative result for progesterone receptor; and (H) negative result for immune checkpoint molecule programmed death-ligand 1. Scale bar, 20 μm. Arrows indicate the typical staining pattern.

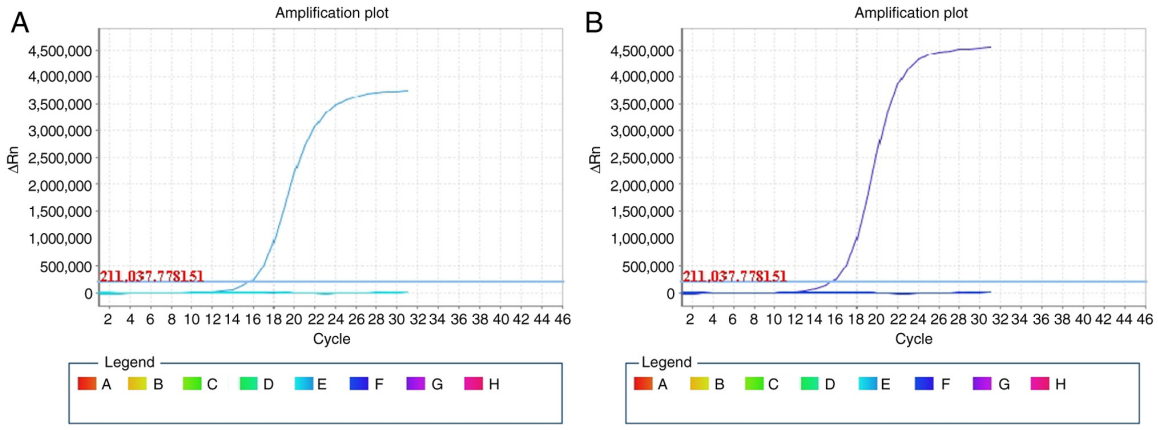

Figure 3. Amplification refractory mutation system-based PCR measurement of wild-type and mutant-type K-ras. (A and B) Real-time amplification dynamic curves of the PCR amplified DNA samples from the lesions of (A) patient 1 and (B) patient 2. The wild-type and the following mutations were tested for: The nucleotide coding for glycine on codons 12 and 13 to mutated to aspartate, alanine, valine, serine, arginine, or cycteine; the nucleotide coding for glutamine on codon 61, mutated to lysine, leucine, arginine or histidine; the nucleotide coding for lysine on codon 117, mutated to asparagine; and the nucleotide coding for alanine on codon 146, mutated to threonine, valine or proline. PCR, polymerase chain reaction. The square symbols with different colors were defined as the wells in the plate for amplification of the wild-type and the five mutants of K-ras. ΔRn on y-axis is the difference of fluorescence intensity during any time point of amplification against the baseline level. Data are representative of independent tests repeated at least three times.

origin. At the molecular level, the occurrence of malignancies is driven by the action of multiple cancer-related genes. In adenocarcinoma and GEA, the accumulation of changes in cancer-related genes could replace the tumorigenic potential of HPV. This substitution propels the initiation of the carcinogenesis process from the host cells' phenotype. Morphologically, gastric-type adenocarcinomas show considerable overlap but must be distinguished from other adenocarcinomas, such as those originating in the pancreas and biliary tract (17).

Microscopically, adenocarcinoma cells closely resemble those of pancreaticobiliary mucinous carcinoma rather than having a gastric origin (17,20). The tumors in the present study were composed of cysts lined with mucinous cells. Immunohistochemically, the cases were negative for p16 and positive for mutant p53. Other positive immunophenotypic markers include CK7 and MUC5AC. Negative immunomarkers included ER and PR. Previous reports indicate that ER and PR expression is absent in the immunophenotype of adenoma malignum (21,22).

In endocervical adenocarcinoma, MUC5AC showed positive expression to varying degrees in the majority of samples analyzed, with some cases being negative similar to previously reported results (23-25).

Similar to previously reported findings, CK7 was positive in the tumors from the present patients (26,27). PD-L1 was negative in the present study, suggesting the status of the host antitumor immunity. High expression of the immune response checkpoint factor implies a restoration of host immunity against tumors, and patients whose tumors overexpress PD-L1 have improved clinical outcomes with anti-PD-1-directed therapy (28).

PAX8 immunoreactivity has proven useful in distinguishing non-gynecological adenocarcinomas. While there have been several studies about GAS (29,30), little is known about the distinguishing features of GAS. Therefore, more studies on the diagnosis of GAS should be reported in the future. PAX8, a paired-box gene crucial in the embryogenesis of the thyroid gland, kidney and Mullerian system, is positive in normal thyroid, renal and Mullerian epithelia, as well as in most carcinomas arising in these organs (29). It has been demonstrated that nuclear PAX8 staining is present in a large number of non-serous ovarian epithelial neoplasms and cervical epithelial lesions (29).

In the present study, PAX8 was found to be negative only in case 1. In the female genital tract, most adenocarcinomas of the ovary, fallopian tube, endometrium and cervix are positive for PAX8. However, primary mucinous adenocarcinomas of the ovary are usually negative, or at most, they exhibit focal weak immunoreactivity. Cervical adenocarcinomas are less likely to be positive than endometrial adenocarcinomas and non-mucinous ovarian adenocarcinomas (30).

Mutant K-ras was not detected in the present study using specimens from two cases of GEA. Given the small amount of material used, the role of a ras gene mutation in the genesis of this specific type of tumor cannot be excluded. Further validation with materials from more cases is required. It has been reported that the frequency of codon 12 mutations of K-ras is high in primary adenocarcinomas of the pancreas, with >80% of the examined carcinomas harboring a point mutation (9,10).

In summary, several relevant histochemical markers have been detected in the present study. The findings generally align with the profile of GEA, but some indicators may vary in different reports. This prompts further screening for more specific markers for the diagnosis of GEA, given its status as a rare clinical entity.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JZ and XZ conceived the idea of investigation, designed the study and prepared the first draft of the manuscript. JZ, XZ, WM, YZ, LY, JJ and MZ reviewed the specimens, confirmed the diagnosis, analyzed the data, and corrected the manuscript. JZ performed the immunohistochemical staining and collected the clinical specimens. JZ, XZ and WM confirm the authenticity of all the raw data. All authors have read and approved the final manuscript, and approved the submission.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Lishui Central Hospital (Lishui, China; approval no. 2023-526).

Patient consent for publication

The patient provided written informed consent for publication of the case study described.

Competing interests

The authors declare that they have no competing interests.

References

1. Adegoke O, Kulasingam S and Virnig B: Cervical cancer trends in the United States: A 35-year population-based analysis. J Womens Health (Larchmt) 21: 1031-1037, 2012.
2. Guo F, Cofie LE and Berenson AB: Cervical cancer incidence in young U.S. females after human papillomavirus vaccine introduction. Am J Prev Med 55: 197-204, 2018.
3. Bewley S: HPV vaccination and cervical cancer screening. Lancet 399: 1939, 2022.
4. Michels KB and zur Hausen H: HPV vaccine for all. Lancet 374: 268-270, 2009.
5. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, *et al*: Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. Lancet 374: 301-314, 2009.

6. Cree IA, White VA, Indave BI and Lokuhetty D: Revising the WHO classification: Female genital tract tumours. Histopathology 76: 151-156, 2020.
7. Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M and Nishimura R: Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. Am J Surg Pathol 31: 664-672, 2007.
8. Mikami Y and McCluggage WG: Endocervical glandular lesions exhibiting gastric differentiation: An emerging spectrum of benign, premalignant and malignant lesions. Adv Anat Pathol 20: 227-237, 2013.
9. Carpenter KM, Durrant LG, Morgan K, Bennett D, Hardcastle JD and Kalsheker NA: Greater frequency of K-ras Val-12 mutation in colorectal cancer as detected with sensitive methods. Clin Chem 42 (6 Pt 1): 904-909, 1996.
10. Hruban RH, van Mansfeld AD, Offerhaus GJ, van Weering DH, Allison DC, Goodman SN, Kensler TW, Bose KK, Cameron JL and Bos JL: K-ras oncogene activation in adenocarcinoma of the human pancreas. A study of 82 carcinomas using a combination of mutant-enriched polymerase chain reaction analysis and allele-specific oligonucleotide hybridization. Am J Pathol 143: 545-554, 1993.
11. Staratschek-Jox A, Kotkowski S, Belge G, Rudiger T, Bullerdiek J, Diehl V and Wolf J: Detection of Epstein-Barr Virus in Hodgkin-ReedSternberg Cells: No evidence for the persistence of integrated viral fragments inLatent membrane protein-1 (LMP-1)-negative classical Hodgkin's disease. Am J Pathol 156: 209-216, 2000.
12. Carleton C, Hoang L, Sah S, Kiyokawa T, Karamurzin YS, Talia KL, Park KJ and McCluggage WG: A detailed immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas. Am J Surg Pathol 40: 636-644, 2016.
13. Zhao S, Hayasaka T, Osakabe M, Kato N, Nakahara K, Kurachi H, Fukase M, Katayama Y, Yaegashi N and Motoyama T: Mucin expression in nonneoplastic and neoplastic glandular epithelia of the uterine cervix. Int J Gynecol Pathol 22: 393-397, 2003.
14. Fan XY, Hu ZY, Xu FH, Yan ZQ, Guo SQ, and Li ZM: Rapid Detection of rpoB gene mutations in rifampin-resistant mycobacterium tuberculosis isolates in shanghai by using the amplification refractory mutation system. J Clin Microbiol 41: 993-997, 2003.
15. Levine AJ, Hu W and Feng Z: The P53 pathway: What questions remain to be explored? Cell Death Differ 13: 1027-1036, 2006.
16. Muller PA and Vousden KH: p53 mutations in cancer. Nat Cell Biol 15: 2-8, 2013.
17. Talia KL and McCluggage WG: The developing spectrum of gastric-type cervical glandular lesions. Pathology 50: 122-133, 2018.
18. Park KJ: Cervical adenocarcinoma: Integration of HPV status, pattern of invasion, morphology and molecular markers into classification. Histopathology 76: 112-127, 2020.
19. Ishii K, Hosaka N, Toki T, Momose M, Hidaka E, Tsuchiya S and Katsuyama T: A new view of the so-called adenoma malignum of the uterine cervix. Virchows Arch 432: 315-322, 1998.
20. Chou YY, Lin MC and Huang LW: Human papillomavirus-unrelated gastric type of cervical adenocarcinoma presenting with a metastatic ovarian tumor: Report of a case. J Low Genit Tract Dis 17: 218-222, 2013.
21. Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, Pike MC, Soslow RA and Park KJ: Gastric-type endocervical adenocarcinoma. An aggressive tumor with unusual metastatic patterns and poor prognosis. Am J Surg Pathol 39: 1449-1457, 2015.
22. Toki T, Shiozawa T, Hosaka N, Ishii K, Nikaido T and Fujii S: Minimal deviation adenocarcinoma of the uterine cervix has abnormal expression of sex steroid receptors, CA125, and gastric mucin. Int J Gynecol Pathol 16: 111-116, 1997.
23. Li H, Jing X, Yu J, Liu J, Zhang T, Chen S and Zhang X: A combination of cytokeratin 5/6, p63, p40 and MUC5AC are useful for distinguishing squamous cell carcinoma from adenocarcinoma of the cervix. Diagn Pathol 15: 104, 2020.
24. Riethdorf L, O'Connell JT, Riethdorf S, Cviko A and Crum CP: Differential expression of MUC2 and MUC5AC in benign and malignant glandular lesions of the cervix uteri. Virchows Arch 437: 365-371, 2000.
25. Hebbar V, Damera G and Sachdev GP: Differential expression of MUC genes in endometrial and cervical tissues and tumors. BMC Cancer 5: 124, 2005.
26. Gilks CB, Young RH, Aguirre P, DeLellis RA and Scully R: Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol 13: 717-729, 1989.
27. McCluggage WG, Shah R, Connolly LE and McBride HA: Intestinal-type cervical adenocarcinoma in situ and adenocarcinoma exhibit a partial enteric immunophenotype with consistent expression of CDX2. Int J Gynecol Pathol 27: 92-100, 2008.
28. Patel SP and Kurzrock R: PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 14: 847-856, 2015.
29. Laury AR, Perets R, Piao H, Krane JF, Barletta JA, French C, Chirieac LR, Lis R, Loda M, Hornick JL, *et al*: A comprehensive analysis of PAX8 expression in human epithelial tumors. Am J Surg Pathol 35: 816-826, 2011.
30. Yemelyanova A, Gown AM, Wu LS, Holmes BJ, Ronnett BM and Vang R: PAX8 expression in uterine adenocarcinomas and mesonephric proliferations. Int J Gynecol Pathol 33: 492-499, 2014.