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Original Research

Clinical Diagnosis and Treatment Analysis of 16 Cases of Gastric-Type Endocervical Adenocarcinoma

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Abstract

Objective: Cervical cancer classification based on human papillomavirus (HPV) infection status is necessary, as the popularity of HPV vaccination is increasing. Hence, this study aimed to explore the clinicopathological features, diagnosis, treatment, and prognosis of gastric-type endocervical adenocarcinoma (GAS) in west China. **Methods**: We performed a retrospective analysis and follow-up of patients with GAS who were hospitalized in West China Second University Hospital, a tertiary care center in west China, between September 2019 and April 2021. **Results**: A total of 16 cases were pathologically diagnosed as GAS at the hospital, most of which had no specific clinical manifestations. Among the 16 cases, 3 cases were confirmed preoperatively. The occurrence of full-layer cervix stroma infiltration, lymphatic vessel infiltration, and lymph node metastasis were 87.5%, 100%, and 50%, respectively. Among all cases, 8 cases were classified as stage III according to the International Federation of Gynecology and Obstetrics 2018 Clinical Staging Standard for cervical cancer. A total of 15 patients underwent a transabdominal or laparoscopic extensive hysterectomy, and the remaining 1 patient was pathologically diagnosed with GAS after a total hysterectomy and afterward underwent bilateral oophorectomy and pelvic lymph node dissection as supplementary surgeries. The follow-up data presented the survival of the 16 patients receiving concurrent chemoradiotherapy after surgery. However, GAS recurred in 3 non-medically-controlled patients among the 16 patients in 3 to 6 months after the treatment. **Conclusions**: GAS is a rare but highly malignant cancer that usually results in a poor prognosis. A few reports of GAS diagnosis and treatment, especially from developing countries, are available. Hitherto clinical routine screening methods might be insufficient to fulfill the requirements of GAS diagnosis owing to the difficulties in preoperative diagnosis and the probability of misdiagnosis. To reduce the rate of misdiagnosis, repeated deep multisite biopsies, cervical curettage, cervical conization, and hysteroscopy might be helpful in suspicious GAS cases.

Keywords: cervical cancer; gastric-type endocervical adenocarcinoma; minimal deviation adenocarcinoma; human papillomavirus-associated cervical cancer

1. Introduction

Gastric-type endocervical adenocarcinoma (GAS) is an HIK1083-positive subset of cervical adenocarcinoma. Kojima and his team from Japan proposed the concept of GAS in 2007 for the first time [1] and described it as a malignant cervix epithelial tumor morphologically similar to the pyloric gland epithelium, expressing gastric mucosa. As a gastric type of cervical mucinous adenocarcinoma, GAS is a rare mucinous adenocarcinoma with morbidity accounting for l%–3% of morbidity in cervical adenocarcinomas and 0.15%–0.45% of morbidity in all cervical cancers. The International Endocervical Adenocarcinoma Criteria and Classification (2018) divided cervical cancers into two categories: human papillomavirus (HPV)-associated (HPV-A) cervical cancer and HPV-independent (HPV-I) cervical cancer. GAS is frequently irrelated to high-risk HPV infection, regarding it as a common subtype of HPV-I cervical cancers. Several cervical cancer subtypes are not caused by HPV. Cervical cancer is a heterogeneous group of neoplasms that indicates different etiology, pathogenesis, molecular changes, treatment response, and prognosis in different subsets. As the majority and popularity of HPV vaccination are increasing today, classifying cervical cancers per the infection status of HPV is essential [2]. GAS exhibits strong invasiveness and poor prognosis with precursors such as atypical lobulated cervical glandular hyperplasia and gastric carcinoma *in situ* [3]. Earlier, a well-differentiated subtype used to be referred to as minimal deviation adenocarcinoma (MDA); however, today, it is no longer recommended [4]. With the wide application of the HPV vaccine, the incidence rate of HPV-A cervical cancer is gradually decreasing. Moreover, the timely recognition and treatment of HPV-I cervical cancer are crucial for reducing the morbidity and mortality rates of cervical

cancers. GAS often lacks specific clinical manifestations, and its histopathological characteristics seem to be similar to benign lesions, which are different from ordinary cervical cancers; this poses a great challenge to clinicopathological diagnosis, especially in an early stage, leading to missed and delayed diagnosis, seriously affecting the prognosis of patients.

At present, a few reports about GAS clinical cases available worldwide are individual case reports. Therefore, in this study, we performed a systematic analysis and follow-up of the diagnosis and treatment of 16 patients with GAS (including 1 patient with MDA) at our hospital. Furthermore, relevant factors that affected the diagnosis, treatment, and prognosis of GAS were thoroughly discussed on the basis of a clinical case review and literature analysis.

2. Data and Methods

2.1 Clinical Data

The clinical case data of patients who were pathologically diagnosed with GAS from September 2019 to April 2021 at the second West China University Hospital of Sichuan University were retrieved. A total of 16 patients were eligible for the study.

Pathological diagnostic criteria were based on the WHO classification of tumors, female genital tumors, 5th edition [5]. Essential: abundant pale eosinophilic to clear cytoplasm and distinct cell borders (gastric phenotype) or well-formed glands with a random distribution and minimal atypia (minimal deviation); destructive invasion and moderate to severe nuclear atypia (gastric-type); negative ER/PR. Desirable: negative or patchy p16 and/or negative HPV testing; neutral-type mucin (pinkish-red on Alcian blue/PAS staining); abnormal p53 staining in ~50% [5].

The results of all pathological tests were reviewed and verified by two pathologists.

2.2 Methods

The clinical manifestations, diagnosis, treatment, and other case data of the 16 patients with GAS were retrospectively analyzed. All patients were followed up by telephone or outpatient visits for 11.23 $\pm$ 5.23 (range, 3–21) months before June 1, 2021. The clinical data of the patients with 16 GAS are presented in Table 1.

3. Results

3.1 Basic Information

The mean age of the 16 patients was 52.94 $\pm$ 10.23 (range, 34–68) years. The main clinical manifestations were irregular vaginal bleeding (8 cases), heavy and transparent vaginal discharge with no peculiar smell (6 cases), physical examination (1 case), and abdominal mass (1 case) caused by ovary metastasis. Postoperative pathology was as follows: 15 cases were of GAS, and 1 case was of MDA.

3.2 Diagnosis and Treatment

Before surgeries, cervical exfoliated cells of the 16 patients were examined, and the thin-prep cytology test (TCT) was indicated in 6 abnormal cases (37.5%) and 2 HPV-positive cases (case 4 and case 5). Consistent with previous findings [6,7], tumor marker levels were abnormal in 9 out of 10 examined cases in the present study, suggesting tumor markers such as CA 125 and CA 19–9 are valuable for GAS diagnosis. Moreover, similar to other pelvic tumors in women [8], GAS may show the first symptom of a giant abdominal mass, as shown by case 3 in this study. According to pathological diagnosis, 9 cases that had been considered as cervical adenocarcinoma by cervical biopsy were confirmed as GAS by postoperative pathology. Two cases were diagnosed as GAS by preoperative cervical biopsy and another one by preoperative fractional curettage. Two adenocarcinoma cases were diagnosed as GAS after surgery, whereas one case that had been considered as the case of an ovarian malignant tumor previously was corrected as GAS (stage IIIC2) after surgery. One case was identified as MDA after a total hysterectomy for adenomyosis.

In terms of treatment, 8 patients underwent a transabdominal extensive hysterectomy, 7 patients underwent a laparoscopic extensive hysterectomy, and one patient with adenomyosis underwent a laparoscopic total hysterectomy and bilateral salpingectomy, followed by a laparoscopic hysterectomy, bilateral oophorectomy, and pelvic lymph node dissection with para-aortic lymph node dissection after the surgery. All patients received concurrent chemoradiotherapy (CCRT) after the operation; 14 patients received it at our hospital, and 2 patients received it at their local medical institutions. The patients were followed-up postoperatively, and all patients survived. However, GAS recurred in 3 patients 3 to 6 months after the treatment. These 3 patients are currently undergoing radiotherapy or chemotherapy.

Based on the International Federation of Gynecology and Obstetrics (FIGO) 2018 Clinical Staging Standard for cervical cancer, 4 cases were of IB (25%), 4 cases of II (25%), and 8 cases of III (50%) stages. The 3 recurrent cases with no medical control were all defined as stage III.

3.3 Pathological Results

The pathological data of the 16 patients with GAS are presented in Table 2. The pathology of 15 patients with GAS showed that in all highly differentiated cervical mucinous adenocarcinoma (gastric patterns), the cervical stroma and tumor thrombi were found in vessels, indicating significant local infiltration. One patient with MDA showed the tumor, infiltrating the whole layer of the cervical stroma and invading the lower segment of the corpus uteri. Besides, lymph-node metastasis was detected in 8 patients. MDA is the best-differentiated type of gastric adenocarcinoma, which is now uniformly called GAS. In this study, patients with GAS tended to be in an advanced stage at the time of

Table 1. Clinical data of 16 patients.

Case	Age	Clinical symptoms	Tumor marker	HPV	TCT	Diagnosis process	FIGO stage	Operation mode	Supplementary treatment	Follow-up
1	63	Vaginal fluid	CA125: <2 U/mL CA199: 8.1 U/mL	Negative	/	Curettage adenocarcinoma, postoperative diagnosis confirmed	$IIIC_1$	RHBSO	Synchronous radiotherapy & chemotherapy	In treatment
2	43	Contact bleeding	CA125: 11.3 U/mL CA199: 69.9 U/mL	/	/	Cervical biopsy, preoperative diagnosis as GAS	IB_3	RHBSO	Synchronous radiotherapy & chemotherapy	In treatment
3	58	Pelvic space occupying 10+ cm	CA125: 74.8 U/mL CEA 42.3 ng/mL CA199: 55.3 U/mL	/	/	Ovarian cancer suggested before operation and diagnosed after operation	$IIIC_1$	RHBSO	Synchronous radiotherapy & chemotherapy	In treatment
4	49	Vaginal fluid	CA125: 8.7 U/mL CA199: 29.3 U/mL	16+	Atypical glandular epithelial cells found	Cervical biopsy, preoperative diagnosis as gastric adenocarcinoma	IB_3	Lap RHBSO	Synchronous radiotherapy & chemotherapy	In treatment
5	61	Vaginal fluid	CA125: 90.2 U/mL CEA 20 ng/mL CA199: 2394.8 U/mL	16+	Atypical squamous epithelial cells of unknown significance found	Segmental diagnosis and curettage suggest adenocarcinoma and postoperative confirmation	$IIIC_2$	RHBSO	Back to local hospital	No recurrence
6	56	Postpartum hemorrhage	/	/	Atypical glandular cells	Segmental diagnosis and curettage, preoperative suggestions of gastric adenocarcinoma	IIB_2	RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence
7	67	Vaginal fluid	/	Negative	Negative	Cervical biopsy suggested adenocarcinoma, confirmed after operation	$IIIC_2$	Lap RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence
8	61	Postpartum hemorrhage	/	/	/	Cervical biopsy suggested adenocarcinoma, confirmed after operation	IB_2	Lap RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence

Table 1. Continued.

Case	Age	Clinical symptoms	Tumor marker	HPV	TCT	Diagnosis process	FIGO stage	Operation mode	Supplementary treatment	Follow-up
9	55	Postmenopausal hemorrhage	/	/	/	Cervical biopsy suggested adenocarcinoma, confirmed after operation	IIB	Lap RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence
10	34	Intraatrial hemorrhage	CA199: 369.7 U/mL	Negative	Negative	Cervical biopsy suggested adenocarcinoma, confirmed after operation	$IIIC_2$	Lap RHBSO	Synchronous radiotherapy & chemotherapy	Recurrence 3 months after chemotherapy
11	44	Increased vaginal secretions	CA125: 50.8 U/mL CA199: 89.9 U/mL	/	Atypical glandular epithelial cells with unclear significance	Cervical biopsy suggested adenocarcinoma, confirmed after operation	$IIIC_1$	RHBSO	Synchronous radiotherapy & chemotherapy	Recurrence 6 months after chemotherapy
12	39	Vaginal fluid	CA125: 74.8 U/mL CA199: 139.9 U/mL	/	/	Cervical biopsy suggested adenocarcinoma, confirmed after operation	$IIIC_1$	RHBSO	Synchronous radiotherapy & chemotherapy	Recurrence 6 months after chemotherapy
13	55	Postpartum hemorrhage	/	Negative	High squamous intraepithelial lesion HSIL	Cervical biopsy suggested adenocarcinoma, confirmed after operation	$IIIC_1$	Lap RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence
14	68	Physical examination	CA125: 8.0 U/mL CA199: 6.8 U/mL	/	Atypical glandular cells, tumor prone	Cervical biopsy suggested adenocarcinoma, confirmed after operation	IB_2	RHBSO	Synchronous radiotherapy & chemotherapy	No recurrence
15	55	Postmenopausal hemorrhage	/	Negative	Negative	Cervical biopsy suggested adenocarcinoma, confirmed after operation	IIA_1	Lap RHBSO	Synchronous radiotherapy & chemotherapy	In treatment
16	43	Irregular vaginal bleeding	No abnormality found	Negative	Negative	Adenomyosis of uterus, Confirmed after total resection	IIA_1	Lap THBSO	Concurrent chemoradiotherapy	In treatment

Table 2. Pathological features of gastric-type endocervical adenocarcinomas.

Case	FIGO stage	(CxSI)	(LVI)	(LNM)	Immunohistochemistry
1	$IIIC_1$	Full layer of cervix stroma	Yes	Yes	P16+, CK7+, MUC-6 Part+, ER-, PR-, CK20-, SATB2-, ki67 positive rate about 30%
2	IB_3	Close to full layer of cervix stroma	Yes	No	ER-, PR-, P16-, CK7+++, CEA++, CK20-, MUC-6 Part +++, CDX-2-, SATB2-, ki67 positive rate about 45%
3	$IIIC_1$	Full layer of cervix stroma	Yes	Yes	P53 Mutant Expression, Pax-2-, Pax-8-, P16-, MUC-6+
4	IB_3	Layer 1/3 of cervix stroma	Yes	No	CK7+, CK20-, MUC-6+, CDX-2 Focal+, CEA Focal+, Pax-2-, P16-, Muc-2-, Muc-5 Part+, P53+, ER-, PR-, Vim-, ki67 positive rate about 25%
5	$IIIC_2$	Full layer of cervix stroma	Yes	Yes	ER-, PR-, CK7+, CK20-, Muc-2-, Muc-5+, Muc-6+, CDX-2 Part+, SATB2-, P16-, CEA+, Vim-, ki67 positive rate about 60%
6	IIB_2	Full layer of cervix stroma	Yes	No	CK7+, CK20-, ER-, PR-, Pax-2-, Pax-8-, Muc-2-, Muc-5+, MUC-6+, Vim-, P16-, ki67 positive rate 60%
7	$IIIC_2$	Full layer of cervix stroma	Yes	Yes	CK7+++, CK20-, Muc-5+++, MUC-6+++, Muc-2-, ER-, PR-, P16-, CEA+, Pax-8+++, CDX-2-, SATB2-, Pax-2-, P53 (+, Wild Type), ki67 positive rate about 40%
8	IB_2	Full layer of cervix stroma	Yes	No	ER-, PR-, CK7+, CK20-, Muc-2-, Muc-5+, Muc-6+, CDX-2-, SATB2-, P16-, ki67 positive rate about 40%
9	IIB	Full layer of cervix stroma	Yes	No	CK7+, CK20-, ER-, PR-, CEA Part+, Vim-, P16-, MUC2-, MUC5 Part+, MUC-6+, Pax-2-, Pax-8+, P53+, CDX-2 Minority+, Villin+, Ki67 positive rate 30%
10	$IIIC_2$	Full layer of cervix stroma	Yes	Yes	CEA Focal+, P16-, ER-, PR-, MUC-6+, Muc-2-, Muc-5+, CK7+, CK20-, CDX-2-, SATB2 ±, Pax-2-, ki67 positive rate about 30%
11	$IIIC_1$	Full layer of cervix stroma Combined focal CINIII	Yes	Yes	Cervical mucinous adenocarcinoma area IHC: CK7+, CK20-, ER-, PR-, CEA-, CDX-2 small focus+, p16-, Villin+, CA125-, Vim+, ki67 positive rate about 30% Mucinous adenocarcinoma of ovary IHC: CK7+, CK20-, P16-, CDX-2 small focus+, Villin focus+
12	$IIIC_1$	Full layer of cervix stroma	Yes	Yes	P16-, ER-, PR-, CEA-, Ki67 positive rate about 40%
13	$IIIC_1$	Full layer of cervix stroma	Yes	Yes	ER-, PR-, P16-, CEA Focus+, Vim-, CK20-, CDX-2-, Villin+++, CA125 focus+, SMA Interstitial+, Ki67 positive rate about 80%
14	IB_2	Layer 1/3 of cervix stroma	Yes	No	ER+, PR-, CEA focus+, P16-, P53+, Ki67 positive rate about 35%
15	IIA_1	Full layer of cervix stroma	Yes	No	CK7+++, CK20-, P16 focus+, Pax-8+, Muc-2-, Muc-5+, Muc-6++, ER-, PR-, Pax-2-, SATB2-, ki67 positive rate about 25%. HPV Typing Detection: 23 subtypes were negative
16	IIA_1	Full layer of cervix stroma	Yes	No	/

CxSI, Cervix Stroma infiltration; LVI, Lymphatic Vascular Infiltration; LNM, Lymph Node Metastasis.

Table 3. Immunohistochemical results of gastric-type endocervical adenocarcinomas.

	CK7	MUC-6	MUC-5	Ki67	ER	PR	MUC-2	SATB2	p53	P16	CK20	CEA	VIM
Cases detected	11	11	8	14	14	14	8	6	3	15	12	10	6
Positive cases	11	11	8	14	1	0	0	1	3	2	0	7	1
Positive rate	100%	100%	100%	100%	7.1%	0%	0%	16.6%	100%	13%	0%	70%	16.6%

CK, Cytokeratin; MUC, Mucins; ER, Estrogen receptor; PR, Progesterone receptor; STAB2, Special AT-rich sequence Binding protein 2; VIM, Vimentin.

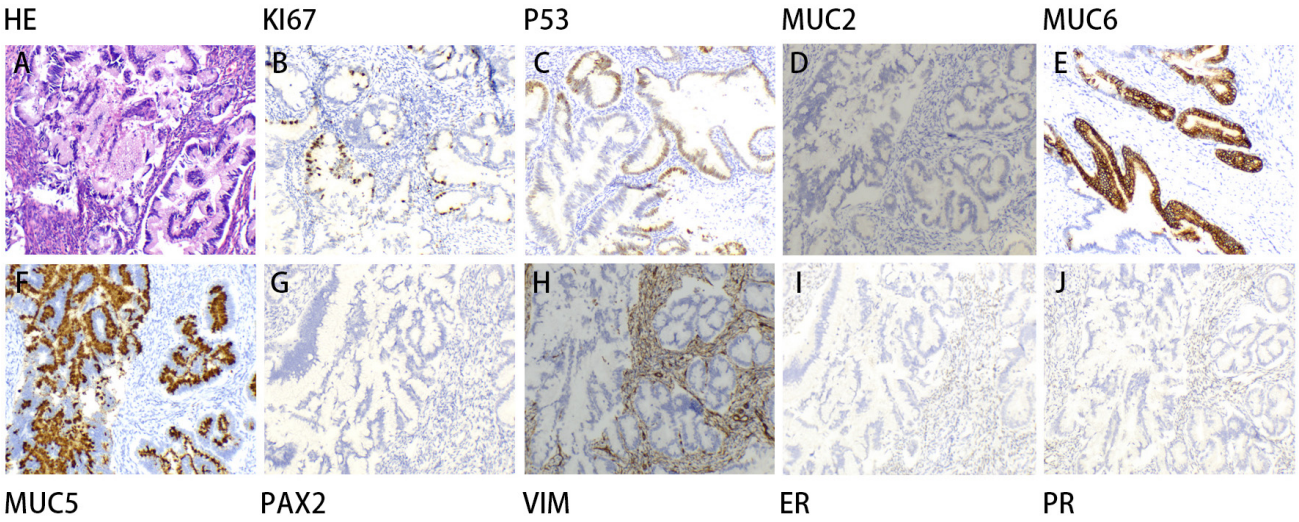

Fig. 1. Histologic characteristics of gastric-type endocervical adenocarcinoma.

visit with a high incidence of deep cervical interstitial infiltration, lymphatic vessel infiltration, and lymph node metastasis, accounting for 87.5% (14/16), 100% (16/16), and 50% (8/16), respectively. The immunohistochemical detection of histopathological sections from patients with GAS showed that the samples were 100% positive for molecular markers such as cytokeratin (CK)7 (11/11), mucin (muc)-6 (11/11), muc-5 (8/8), Kiel (Ki)67 (14/14), and tumor protein P53 (p53) (3/3). The positive rate of carcinoembryonic antigen (CEA) (7/10) was as high as 70%, whereas those of other common molecular markers were relatively low, as shown in Table 3 and Fig. 1.

4. Discussion

GAS was first proposed by Kojima and his Japanese team in 2007 [1]. It is pathologically characterized by the production of gastric mucus. GAS is morphologically similar to the malignant epithelial tumor of the pyloric gland epithelium in the cervix. Compared with other cervical cancers, GAS is highly invasive and resists conventional chemotherapy, which results in an unsatisfactory prognosis that is even worse than that of ordinary cervical adenocarcinomas. The lack of specific clinical manifestations and similarity in pathologic features to benign lesions make the pathological diagnosis of GAS a challenge. The reasons for this are as follows: (1) GAS often lacks specific clinical manifestations. (2) The lesions found in GAS are mostly hidden inside the cervical canal, which renders low positive rates of TCT and cervical biopsy. Therefore, only 3 of the patients in this study were pathologically confirmed by biopsy before surgery, and the remaining patients were confirmed after surgery. (3) Histologically, GAS is frequently well-differentiated, which makes it difficult to distinguish it from other benign diseases. The above characteristics are also the reason why it is challenging to distinguish between neoplastic gastric glands and normal cervical glands during the cervical biopsy. Therefore, missed diagnosis can occur [9]. Due to the highly malignant biological behavior, GAS spreads fast and is commonly found in the late stage at the time of diagnosis. This complicates the treatment and leads to a prognosis poor. Among the enrolled patients, 50% of the patients were in stage III, which was consistent with the percentage of 59% of patients in stage II or above as reported. Previous studies have reported that in patients with ordinary adenocarcinoma, only 11% of the patients were in the advanced stage during diagnosis [10]. Routine screening and pathological examination of cervical cancer seemed insufficient to fulfill the present requirements of GAS diagnosis. Therefore, immunohistochemical markers and other technologies and methods should be used to improve the diagnosis of GAS in the early stage. This will particularly help in the treatment and prognosis of GAS.

4.1 Early Identification and Diagnosis

The difficulty in diagnosis of GAS is reported by a limited number of published research studies and epidemiological data. Women between the age of 30 and 80 can suffer from GAS. Patients show a range of major clinical symptoms such as heavy mucinous, watery vaginal secretions, or irregular vaginal bleeding [11]. Nevertheless, many patients without any specific clinical symptoms were pathologically diagnosed with GAS [12]. GAS is mostly located in the upper part of the cervix and deep inside the cervical glands, unlike ordinary cervical adenocarcinomas. It is highly invasive and spreads to the peritoneum. It invades the ovaries and the greater omentum. The affected tissues can be thickened and hardened, and the cervix becomes barrel-shaped without the presence of any distinct huge mass. Because the mode of growth is endogenous and not exogenous, GAS presents a smooth cervix in the gynecological examination and cannot be discovered via cytology or cervical scraping [13].

Ordinary cervical adenocarcinoma is usually associated with a high risk of HPV18 infection, whereas GAS is not associated with HPV infection, according to present studies. A previous study reported that HPV does not promote this specific subtype of cervical adenocarcinoma. Because HPV is found in the adjacent cervical upper skin in the sensitive polymerase chain reaction (PCR) test of the cervical whole tissue section, false-positive results can occur. When these patients were diagnosed using laser capture microdissection PCR, the HPV detection of tumor cells was always negative [14]. Therefore, we speculated that the 2 HPV-positive patients in this study can be false positives. GAS is associated with lobar endocervical glandular hyperplasia (LEGH) and Peutz-Jeghers syndrome [15]. Cervical gastric adenocarcinoma in situ and atypical LEGH share common molecular genetic alterations, such as deficiency of 1p and acquisition of 3q, and both of them are precancerous lesions of GAS.

GAS is usually discovered accidentally [16]. The low diagnostic rate by routine cytological screening can be due to the difficulty in obtaining material, the nuance of cytology in gastric mucinous adenocarcinoma, and the lack of knowledge about the disease. In the present study, only 6 patients (37.5%) presented abnormalities in TCT, and 3 patients were diagnosed with GAS (18.8%) by preoperative pathological examination, which was significantly lower than that of other types of cervical cancers. Therefore, a deep biopsy of cervical tissues and colposcopic cervical curettage should be performed when GAS is highly suspected clinically. Many of the 12 patients (75%) in stage II or later stages were diagnosed with advanced cancer during their follow-ups. A patient who was admitted to the hospital with a pelvic mass was suspected of having an ovarian malignant tumor. The patient had abnormalities during routine cervical screening and was diagnosed with gastric mucinous adenocarcinoma through cervical biopsy and by examining the frozen section of the ovarian tumor during surgery. Another patient who underwent hysterectomy for adenomyosis had repeated negative results of cervical cytology screening and fractional curettage before surgery; however, the diagnosis was MDA based on the postoperative pathology. Well-differentiated GAS appears to be normal during colposcopy, cervical cytology, and even during the routine histopathological examination. To confirm the diagnosis of GAS, deeper tissues should be collected, or cervical conization should be performed. Because of occult lesions and inaccurate materials, the biopsy diagnosis can be diversified, which includes chronic cervicitis, cervical polyps, atypical hyperplasia of cervical glandular epithelium, and endometrioid adenocarcinoma. These are also the reasons for missed diagnosis. Therefore, for patients with cervical hypertrophy along with vaginal fluid, contact bleeding, or irregular vaginal bleeding, when biopsy results do not match the clinical results, multiple deep biopsies, cervical curettage, hysteroscopy, and even cervical conization should be performed to avoid the missed diagnosis of early GAS.

4.2 Biological Behavior and Pathological Characteristics

In histopathological morphology, GAS seems to be "kind", but it is indeed aggressive. The biggest paradox and challenge of the diagnosis and treatment of dedifferentiated endometrioid adenocarcinoma (DEAC) lies in its biological behaviors. Routine screening and examination for cervical cancer may not fulfill the present requirements of diagnosis. Therefore, pathologists and clinicians should have more understanding and vigilance toward GAS to increase the accuracy of diagnosis and reduce the risk of missed diagnosis or misdiagnosis. Kojima *et al*. [1] proposed the following three morphological criteria: (1) abundant mucinous cytoplasm, (2) transparent or lightly eosinophilic cytoplasm, and (3) a clear cell boundary. In 2019, these criteria were extended by Pirog *et al*. [17] with a pathomorphological description that the glands of DEAC can be composed of small cubic or flat cells, papillary glands, goblet cells in glands, and thick eosinophilic cells characterized by distinct cytoplasmic vacuoles, namely foam-like cytoplasm. Gastric differentiated glands are usually simple in structure, single tubular, and widely distributed in the cervical stroma. Most of its glands differ in size, and most of its glandular cavities are dilated or angular. The cell boundary of the gland is clear; the cytoplasm is rich, transparent, or lightly eosinophilic. The nucleus is light to moderate atypia, and small nucleoli can appear, with few pathological mitotic images or necrosis. The degree of fibrogenic reaction in the surrounding cervical stroma differs. The above characteristics are also the pathological reasons for the complexity in differentiating normal cervical glands from neoplastic gastric glands during cervical biopsy and the higher risk of missed diagnosis. When the cervical gland is more than, or equal to 7 mm below the surface of the cervix and

slightly abnormal glands are close to the thick-wall blood vessels, the pathologists should be alerted to the possibility of GAS, and a timely discussion with the gynecologists is necessary. The pathologists and gynecologists can completely avoid misdiagnosis or missed diagnosis with further knowledge of the clinical manifestations, signs, and auxiliary examinations of the patient by appropriately combining the application of immunohistochemical markers.

GAS shows highly malignant biological behavior, strong invasiveness, and rapid metastasis. Most patients with GAS are found to have metastasis to fallopian tubes, ovaries, or the greater omentum when diagnosed, which makes the treatment more difficult and leads to a poor prognosis. Furthermore, metastasis lesions could be infiltrated with a considerate quantity of neutrophils. In some patients, endometrial involvement and nerve infiltration can occur, and the tumor glands that spread to fallopian tubes and endometrium resemble the benign mucous-metaplasia glands. Advanced techniques and diagnostic markers, such as immunohistochemical markers, should be fully used for the pathological examination, thereby aiming to improve the diagnosis and differential diagnosis of GAS. CK7, CK20, CEA, MUC6, p16, ER, and p53 are common immunohistochemical markers in the diagnosis of gastric adenocarcinoma [18–20]. Patients with GAS are usually positive for HIK1083, CK7, CEA, and MUC6. Among them, HIK1083 is a relatively specific marker for gastric adenocarcinoma; however, its sensitivity is only about 75% [21]. Even though the positive rate of MUC6 is as high as 45.8% to 81.0%, its specificity was reported to be quite low, which can be due to its expression in normal glands (8%) [22–24]. The positive rate of p53 mutant expression ranged between 41.0% and 51.9%. Besides, ER and PR are negative in general. It was reported that 61.7% of 47 patients with gastric adenocarcinoma were p16 negative, with 29.7% showing focal expression and 4.3% showing cytoplasmic expression [25]. Similarly, p16 has a high negative rate (86.7%, 13/15) and a low positive rate in the present study. Even though GAS is irrelevant in HPV infection, its pathogenesis and molecular genetic characteristics should be studied further.

4.3 Treatment Strategies

Most of the guidelines for the treatment of cervical cancers are based on the treatments for cervical squamous cell carcinoma and common cervical adenocarcinoma. HPV-I cervical adenocarcinoma has different biological behavior and clinical outcomes. Because of low morbidity and insufficient studies with large sample data, GAS lacks specialized standards for its screening, diagnosis, and treatment. Therefore, the treatment regimen for GAS is that of squamous cell carcinoma at the same stage, which is still controversial. Because GAS can spread to the abdominal cavity along the peritoneum, patients with early-stage GAS should receive surgeries similar to the comprehensive staging surgery for early ovarian carcinomas, such as extensive hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, omentectomy, and appendix resection, supplemented by platinum-based CCRT or radiotherapy. In the present study, 14 patients underwent an extensive hysterectomy. One patient was diagnosed with endometrial gastric adenocarcinoma and received laparoscopic panhysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. Another patient was diagnosed with MDA after a total hysterectomy and, thus, underwent bilateral oophorectomy and pelvic and abdominal para-aortic lymph nodes dissection. The 2 patients were supplemented with CCRT after the surgery. The follow-up of the patient with MDA who underwent a series of medical interventions, such as total hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection, and postoperative CCRT rather than extensive hysterectomy, showed an ideal prognosis [26]. A total of 18 patients with MDA were once classified into the early stage (FIGO IB1/IB2, 88.8%) and advanced stage (FIGO III/IV, 11.1%), which indicated that despite the difficulty in diagnosing timely and precisely, the majority of the patients can be detected in their early stages [27]. This was also verified in our study. Although preoperatively, only 3 of 16 patients were confirmed as GAS by biopsy. A total of 14 patients were correctly diagnosed with cervical adenocarcinoma by pathological examination, which supported the possibility of early discovery through preoperative biopsy or sectional curettage. Li *et al*. [28] summarized and reported that the mean survival time for patients in stages I, II, III, and IV were 5 years, 38.1 months, 22.8 months, and 5.4 months, respectively. For early-staged patients who underwent an extensive hysterectomy, the multidisciplinary treatment strategies of cis-platinum-based CCRT and molecular-targeted therapy should be determined for improving the local progress and prognosis of gastric adenocarcinoma. Compared with patients in the early stages, the patients in the middle and advanced stages showed an inferior prognosis. Patients with one stage-IB followed up in our study had no recurrence (18 months after therapies), whereas the patients with 3 stage-IIIC suffered from recurrence within 3 to 6 months after treatment, so they underwent radiotherapy and chemotherapy, and their conditions had been constantly followed up.

5. Conclusions

GAS is a rare cervical mucinous adenocarcinoma. GAS is different from ordinary cervical adenocarcinoma and has similar morphology to benign lesions. It has strong invasiveness and usually results in a poor prognosis. GAS is independent of high-risk HPV infection. So far, no effective technique for the screening, diagnosis, and treatment of GAS has been established. With the popularity of precise screening for HPV-related cervical lesions and the wide application of HPV vaccines, the morbidity of HPV-I diseases such as GAS will increase. The great attention

of clinicians to GAS can help patients with early diagnosis and timely treatment. Clinically, gynecologists should give extra importance to symptoms such as heavy vaginal discharges and cervical hypertrophy. If gastric adenocarcinoma cannot be completely excluded from diagnosis, repeated deep-multisite biopsies of the cervix, curettage of the cervical canal, or cervical conization can be adopted when necessary. In some patients, GAS can only be confirmed after performing a hysterectomy with thorough evaluation and communication. To conclude, to improve the prognosis, further in-depth research is important to clarify the best diagnosis and treatment strategies for GAS. Early screening and individualized treatment strategies can help in GAS research.

Author Contributions

RQD and MZW carried out the retrospective review of all cases, participated in the writing and organization of the manuscript. TYZ and ZYZ participated in the design of the study, and carried out the study and correction of the manuscript. YJZ, YHL participated in the study's design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from each patient for publication of this study and accompanying images (Approval number: 2016020).

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Conflict of Interest

The authors declare no conflict of interest.

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