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ORIGINAL PAPER

Mucinous adenocarcinoma, gastric type of the uterine cervix: clinical features and *HER2* amplification

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Abstract

Mucinous adenocarcinoma, gastric type (GAS) is difficult to diagnose and shows poor prognosis. Trastuzumab, an anti-human epidermal growth factor type 2 (HER2) monoclonal antibody, is effective in HER2-positive stomach cancer. The objectives of this study were to identify the clinicopathological characteristics of GAS and to evaluate HER2 expression in GAS. We retrospectively reviewed 322 cervical cancer cases diagnosed at the Kyoto University Hospital from 2010 to 2016. The incidence, clinical factors including age, stage, and lymph node status, tumor markers, immunoreactive expression of MUC6, HIK1083, and HER2, and *HER2* amplification were evaluated. Of the 322 cases of cervical cancer, 13 cases of the adenocarcinoma cases were diagnosed as GAS. Watery discharge, lower abdominal pain, CA19-9 elevation, and lymph node metastasis were frequently observed in GAS ($p=0.0226$, $p=0.0400$, $p=0.0346$, and $p=0.0274$, respectively). Immunohistochemistry showed positive MUC6 status in all 13 cases and positive HIK1083 status in 8 cases. The HER2 expression status was equivocal in six cases by immunohistochemistry and *HER2* amplification was identified in one case. GAS exhibits frequent lymph node metastasis and clinical symptoms such as watery discharge and lower abdominal pain, high levels of CA19-9. In addition, some parts of GAS exhibit *HER2* amplification.

Keywords Mucinous adenocarcinoma · Gastric type · GAS · Uterine cervical cancer · *HER2* amplification · Clinical feature

Introduction

Mucinous adenocarcinoma, gastric type (GAS) of the uterine cervix is a new disease category described in the 2014 WHO classification. The incidence of GAS is reported to be 20–25% of all adenocarcinomas of the uterine cervix [1]. Due to its pathologically well-differentiated features, it is difficult to distinguish GAS from benign tumors such as lobular endocervical glandular hyperplasia (LEGH) [1]. Although the 5-year survival rate of all types of cervical adenocarcinoma has been reported to be nearly the same as that of squamous cell carcinoma (SCC) [2], and neo-adjuvant chemotherapy is effective in typical cervical adenocarcinoma [3], GAS is chemoresistant. Hence, compared to other types of cervical adenocarcinoma, GAS shows poorer prognosis [4]. Therefore, differentiating GAS from benign tumors and offering timely treatment is very important to improve patient prognosis.

Since GAS of the uterine cervix as a separate disease entity has been established recently, prognostic indicators and biomarkers that can be used to improve prognosis are still unknown. Some previous reports show that chemotherapy-resistant-type stomach cancer was human epidermal growth factor receptor 2 (HER2) positive. Moreover, HER2-positive cases were susceptible to monoclonal HER2 treatment, resulting in improved survival rates in HER2-positive breast cancer and stomach cancer treated with

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anti-HER2 antibody [5]. To date, there is only one study that has explored the status of *HER2* amplification in GAS of the uterine cervix, and hence, this aspect needs to be further elucidated adequately [6].

The aim of this study was to identify the clinicopathological features, prognostic markers and *HER2* amplification status in GAS of the uterine cervix.

Patients and methods

Patient characteristics and pathological review

The institutional ethics committee approved this retrospective study. We retrospectively assessed 322 cervical cancer cases including gastric-type adenocarcinoma diagnosed at the Kyoto University Hospital from January 2010 to March 2016. All patients provided informed consent. Hematoxylin and eosin-stained sections were reviewed by pathologists and gynecologists at the Kyoto University Hospital. Clinical symptoms and age at diagnosis were collected from medical records retrospectively. Uterine cervical cytology was evaluated using the Bethesda system in all cases except for GAS cases that were evaluated in previous clinics. The diagnoses of GAS were morphologically established using the World Health Organization (WHO) classification (2014) and the morphologic criteria described by Kojima et al. [7]. The criteria were as follows: the tumors are composed of cells with (1) clear or pale eosinophilic cytoplasm, (2) voluminous cytoplasm, and (3) distinct cell borders. We excluded cases that expressed tumor suppressor P16 from GAS cases, because GAS is most often not associated with high-risk HPV. Clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) 2008 criteria was applied for all patients [8]. Lymph node metastasis was diagnosed pathologically. Serum tumor markers including squamous cell carcinoma antigen (SCC), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and cancer antigen 19-9 (CA19-9) were measured within 1 month before the primary treatment.

Immunohistochemistry

Immunohistochemical studies suggesting the existence of pyloric gland mucins (MUC6 and HIK1083) were performed. The HER2 expression status was also evaluated. Sections from formaldehyde-fixed, paraffin-embedded tissue were deparaffinized and rehydrated, and immunohistochemical staining was performed using the Ventana BenchMark ULTRA instrument (Ventana Medical Systems, Tucson, Arizona). Antibodies used were as follows: mouse anti-MUC6 antibody (clone: CLH5, 1:100 dilution; Leica Biosystems), mouse anti-HIK1083 antibody (clone: M-GGMC-1, 1:100 dilution; Kanto Chemical Co.), rabbit anti-HER2 antibody (clone: 4B5, PATHWAY, Ventana Medical Systems), rabbit anti-PAX8 antibody (polyclonal, 1:1000 dilution, proteintech), mouse anti-p53 antibody (clone: DO-7, 1:100 dilution, DAKO), and rabbit anti-HNF1B antibody (polyclonal, 1:1000 dilution, Atlas Antibodies).

Membranous and cytoplasmic staining for MUC6 and HIK1083 indicated positive staining status. The criteria for gastric cancer described by ASCO/CAP guideline on HER testing were applied to evaluate HER2 expression in GAS cases. The immunohistochemical staining intensity was scored a value from 0 to 3+. Samples with equivocal immunohistochemical results (2+) were further analyzed by dual color hybridization (DISH) assay for amplification of the *HER2* gene.

DISH (dual color in situ hybridization) assay

The DISH assay for the *HER2* gene is a technique designed to determine *HER2* status by detecting *HER2* gene copies via silver in situ hybridization and chromosome 17 copies via chromogenic red in situ hybridization on a single slide. If the *HER2*:CEP17 ratio was more than 2.0, the cases were categorized as positive for amplification.

Statistical methods

Fisher's exact test was used to determine differences in the distribution of the clinical factors (FIGO stage, lymph node metastasis, and tumor markers). The Mann–Whitney *U* test was used to analyze differences in ages between patients with GAS and non-GAS carcinoma. A p value of <0.05 was considered statistically significant.

Results

Clinical characteristics and evaluation of gastric and non-gastric types

Of 322 cases of cervical cancer, squamous cell carcinoma (SCC) accounted for 223 cases (69.3%), adenocarcinoma for 69 cases (21.4%), and adenosquamous cell carcinoma for 15 cases (4.7%). Thirteen cases (4.0% of all cervical cancer and 18.8% of adenocarcinoma) were diagnosed as invasive GAS. In adenocarcinoma cases, there was no significant difference between GAS cases and non-GAS cases with regard to age and stage of disease ($p=0.7963$ and $p=0.6551$, respectively; Table 1). Eight out of 13 GAS cases (61.5%) and 28 out of 54 non-GAS cases (51.9%) complained of abnormal genital bleeding or contact bleeding, although the difference was not statistically significant ($p=0.7578$, Table 1). However, watery

Table 1 Summary of the characteristics of patients with gastric-type and non-gastric-type adenocarcinoma

	Gastric type ($N=13$)	Non-gastric type ($N=56$)	p value
Age			
Median	51.2 (38–72)	50.6 (31–82)	0.7963
Stage			
Stage I	6	37	0.6551
Stage II	3	8	
Stage III	2	2	
Stage IV	1	9	
Chief complaints			
Abnormal genital bleeding, contact bleeding	8 (61.5%)	28 (51.9%)	0.7578
Watery discharge	4 (30.8%)	3 (5.6%)	0.0226*
Lower abdominal pain	4 (30.8%)	4 (7.4%)	0.0400*
Abnormal vaginal secretion	0	2 (3.7%)	1.0000
Dysuria	0	2 (3.7%)	1.0000
Abdominal distention	0	2 (3.7%)	1.0000
External genital itching	0	1 (1.9%)	1.0000
Cough	0	1 (1.9%)	1.0000
Anorexia	0	1 (1.9%)	1.0000
No complaints	0	16 (29.6%)	0.0282*
Cytology			
Adenocarcinoma	5 (45.5%)	31 (58.5%)	
AGC	3 (27.3%)	8 (15.1%)	
AIS	0	4 (7.5%)	
SCC	0	3 (5.7%)	
HSIL	0	1 (1.9%)	
ASC-H	0	2 (3.8%)	
Class 3	1 (9.1%)	0	
ASC-US	0	1 (1.9%)	
Unsatisfactory for evaluation	0	1 (1.9%)	
NILM	2 (18.2%)	2 (3.8%)	
Pathology before surgery			
Adenocarcinoma, gastric type	8 (61.5%)	0	
Adenocarcinoma	4 (30.8%)	43 (81.1%)	
AIS	0	7 (13.2%)	
CIN3	0	1 (1.9%)	
SCC	0	1 (1.9%)	
No malignancy	0	1 (1.9%)	
LEGH	1 (7.7%)	0	
Tumor markers			
SCC			
>1.5 ng/ml	0 (0%)	8 (14.5%)	0.3372
≤ 1.5 ng/ml	13 (100%)	47 (85.5%)	
CEA			
≥ 5 ng/ml	1 (7.7%)	17 (30.4%)	0.1597
<5 ng/ml	12 (92.3%)	39 (69.6%)	
CA125			
≥ 35 U/ml	5 (38.5%)	12 (21.4%)	0.2826
<35 U/ml	8 (61.5%)	44 (78.6%)	

Table 1 (continued)

	Gastric type ($N=13$)	Non-gastric type ($N=56$)	p value
CA19-9			
≥ 35 U/ml	7 (53.8%)	12 (21.4%)	0.0346*
< 35 U/ml	6 (46.2%)	44 (78.6%)	
Lymph node status			
Metastasis absence	5	35	0.0274*
Metastasis presence	5	6	

AGC atypical glandular cells, *AIS* adenocarcinoma in situ, *SCC* squamous cell carcinoma, *HSIL* high grade squamous intraepithelial lesion, *ASC-H* atypical squamous cells—cannot exclude HSIL, *ASC-US* atypical squamous cells of undetermined significance, *NILM* negative for intraepithelial lesion or malignancy, *CIN3* cervical intraepithelial neoplasia grade 3, *LEGH* lobular endocervical glandular hyperplasia

*$p < 0.05$

discharge and lower abdominal pain were more frequent in the GAS group than in the non-GAS group ($p = 0.0226$ and $p = 0.0400$, respectively; Table 1). All GAS patients showed clinical symptoms, whereas 16 non-GAS patients did not present with any clinical symptoms ($p = 0.0282$, Table 1).

Preoperative cervical cytology revealed that nine out of 11 patients (81.8%) in the GAS group were diagnosed as having abnormalities. In the non-GAS group, 50 out of 53 cases (94.3%) showed abnormal findings by cervical cytology (Table 1). These results indicated that there was no statistically significant difference between the GAS and non-GAS groups. In the pathological diagnosis using punched biopsy before the treatment, 8 out of 13 gastric-type cases (61.5%) were diagnosed accurately as gastric-type adenocarcinoma, whereas an accurate diagnosis of adenocarcinoma was issued for 43 out of 53 patients in the non-GAS group (81.1%, Table 1). These findings indicated that GAS was diagnosed less accurately prior to treatment than were other types of carcinomas ($p = 0.0057$).

There was no statistically significance in the status of SCC, CEA, and CA125 expression between GAS cases and non-GAS cases ($p = 0.3372$, $p = 0.1597$, $p = 0.2826$, respectively; Table 1). While none of the GAS cases showed high SCC levels, CA19-9 positivity was significantly more frequent in GAS cases than in non-GAS cases (seven out of 13 versus 12 out of 56, respectively; $p = 0.0346$: Table 1).

Pathological evaluation identified significantly more frequent lymph node metastasis in GAS cases compared to non-GAS-type cases ($p = 0.0274$, Table 1). Lymph node metastatic sites include parametrial, obturator, suprainguinal, external iliac, common iliac, and sacral nodes. Only one patient had para-aortic nodes metastasis. Immunohistochemistry showed positive MUC6 status in all 13 cases of GAS and positive HIK1083 status in 8 GAS cases (Fig. 1c). Five cases were positive for PAX8, two cases were positive for HNF1B, and five cases were positive for p53 (Fig. 1d).

Treatment and prognosis of gastric-type cases

Treatments, regimen of chemotherapy, and therapeutic effect in GAS patients are summarized in Supplementary Table 1. All ten stage I and II cases underwent surgery. Two cases that had not been diagnosed as GAS before surgery received neo-adjuvant chemotherapy using paclitaxel and cisplatin (TP) (cases 6 and 9 in Supplementary Table 1). In response to neo-adjuvant chemotherapy, stable disease was induced in two cases as per Response Evaluation Criteria in Solid Tumors (RECIST), with a concomitant decrease in tumor volume (by 20–25%). The pathological findings in representative cases are presented in Fig. 1a. The morphological features of the biopsied tissue showed irregular tubular glands consisting of atypical cells with hyper-chromatic nuclei, resulting in a diagnosis of a typical adenocarcinoma. This case received neo-adjuvant chemotherapy following surgery (radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy). The pathological findings of the surgically resected tumor showed diffuse infiltration and gastric differentiation, and tubular glands with clear cytoplasm and distinct cell borders (Fig. 1b). Immunohistochemical evaluation revealed gastric features with MUC6 and HIK1083 positivity (Fig. 1c). Eight out of the 10 stage I and II cases received adjuvant chemotherapy. Regimens included TP, paclitaxel and carboplatin (TC), S-1 (tegafur/gimeracil/oteracil), and irinotecan therapies. Adjuvant chemotherapy was not administered in one case due to post-operative complications (case 5 in Supplementary Table 1) and in another case due to low risk of recurrence (case 2 in Supplementary Table 1). The latter case was initially diagnosed as lobular endocervical glandular hyperplasia (LEGH) at the diagnostic conization of the cervix. Two years later, this case was suspected as malignant, because a solid component was identified by magnetic resonance imaging, and hence, the patient underwent surgery. Adjuvant chemotherapy was not administered, because GAS cells co-existed locally with LEGH. Of eight patients who received adjuvant

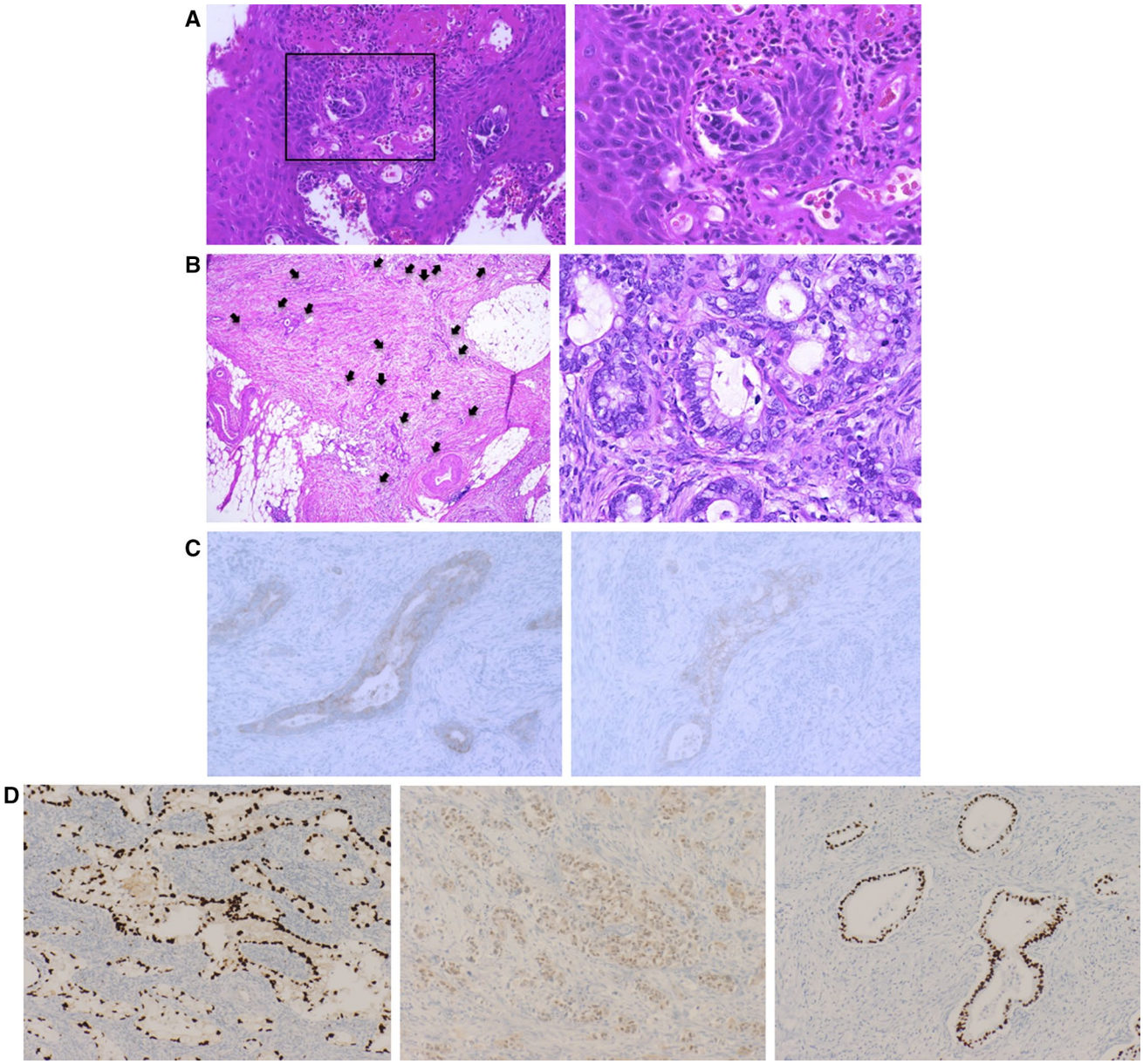

Fig. 1 Microscopic findings and immunohistochemistry of a gastric-type mucinous adenocarcinoma (GAS). **a** Morphological findings of the biopsied tissues before neo-adjuvant chemotherapy (left and right, respectively). **b** Pathology of tissues resected surgically after neo-adjuvant chemotherapy. Well-differentiated cancer cells are seen infiltrating diffusely (arrow in left). **c** Immunohistochemistorical findings of MUC6 (left) and HIK1083 (right) expression. **d** Representative findings of PAX8 (left), HNF1B (middle) and p53 (right) expression

chemotherapy, five patients relapsed. All three cases with stage III and IV disease received systemic chemotherapy, concurrent chemoradiotherapy (CCRT), or surgery including anterior pelvic exenteration and lymphadenectomy (Supplementary Table 1). Of the three patients with stage III and IV disease, only one patient who had received surgery survived, with no evidence of disease. For recurrent cases, CCRT, or systemic chemotherapy including S1 and cisplatin, irinotecan and nedaplatin, S-1, or gemcitabine, was administered. However, all recurrent cases relapsed due to limited efficacy of therapy offered, resulting in stable disease or progressive disease as per RECIST.

HER2 status

We evaluated the HER2 status in 13 cases using immunohistochemistry and DISH. Seven GAS cases exhibited negative HER2 expression (Fig. 2a), whereas the other six cases exhibited equivocal HER2 expression by immunohistochemistry (Fig. 2b). Of the six equivocal cases, DISH was

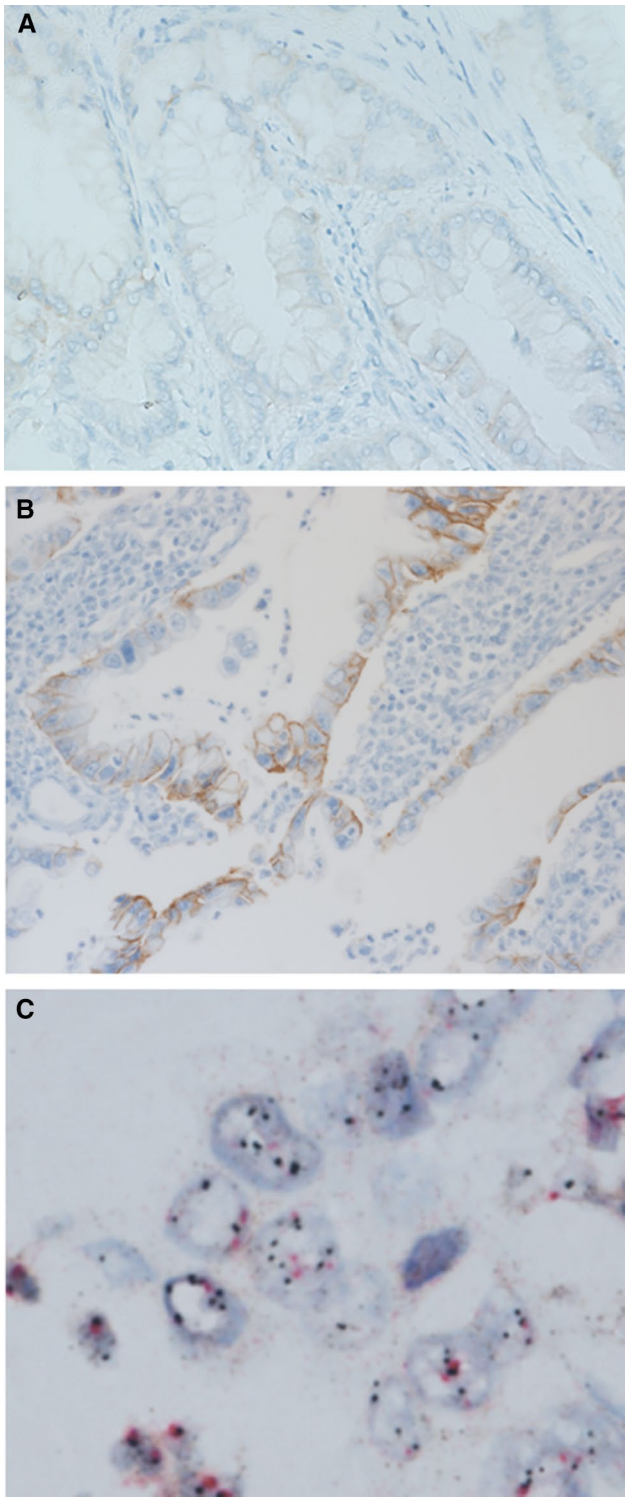

Fig. 2 Evaluation of *HER2* amplification using immunohistochemistry (**a, b**) and dual color in situ hybridization (DISH) (**b**). **a** Negative expression of HER2 using immunohistochemistry. **b** Equivocal expression as observed by immunohistochemistry. **c** Ratio of the *HER2* gene (black dots) signal to the centromere 17 (red dots) signal is more than 2

unsuccessful in two cases, while *HER2* amplification was identified in one case (Fig. 2c).

Discussion

The GAS of the cervix is an aggressive malignant disease, and it is important to diagnose this disease accurately. In our study, the incidence of GAS in adenocarcinoma was 18.8%, which was compatible with the previous reports [9]. Interestingly, the cytological high-risk HPV positivity rate in atypical glandular cells is higher in the USA compared to that in Japan (100 versus 53%), due to a higher prevalence of GAS in Japan [9]. Although our results indicated that GAS was diagnosed less accurately than non-GAS based on morphological features before surgery, 81.8% of GAS cases were diagnosed as abnormal based on cervical cytology. These findings suggest that detecting abnormality in GAS by cytology is effective. In our study, significantly more GAS cases showed watery discharge and lower abdominal pain compared to non-GAS cases. While 29.6% of non-GAS cases were asymptomatic, all GAS cases displayed symptoms. The serum levels of CEA, CA19-9, and CA72-4 have been reported to be effective biomarkers for detecting stomach cancer [10]. Our findings suggested that serum CA19-9 is a more useful marker than CEA in GAS. The previous reports showed that the rates of HIK1083 and MUC6 positivity in GAS are 75–100 and 31–81%, respectively [6, 7, 11] and magnetic resonance imaging (MRI) features of GAS, including endophytic growth, tiny cysts, and upper cervical site, are different from those of the non-GAS type [12]. In addition, other reports have suggested that a combination of MRI, pap smears, and immunohistochemistry (HIK1083 and MUC6) may improve the accuracy of the preoperative diagnosis of minimal deviation adenocarcinoma (MDA) in patients with watery discharge and cysts on the cervix [13]. These findings suggest that watery discharge, lower abdominal pain, high level of serum CA19-9, and endophytic growth in the uterine cervix on MRI are useful predictive markers for GAS. Immunohisotochemical HIK1083 and MUC6 status may help in accurate diagnosis of GAS, and differentiate GAS from other types of adenocarcinoma. Several studies reported that 68–80% of GAS were positive for paired-box 8 (PAX8) which is crucial in embryogenesis of the Mullerian system [6, 14]. HNF1 homeobox B (HNF1B) is positive in 27–93% of GAS, 40–64.5% of usual type adenocarcinoma, and 100% of intestinal adenocarcinoma of the uterine cervix [6, 14, 15]. In addition, p53 exhibits mutation status in 41–51.9% of GAS [6, 14, 15]. These findings are compatible with our results.

In this study, one case was diagnosed as LEGH after conization, and subsequently re-diagnosed as GAS, because solid components had grown during the 2-year follow-up.

Although LEGH is considered as benign (first defined by Nucci et al. [16]), minor subsets of LEGH may function as precursors of GAS due to possible co-existence of malignant lesions [9, 17]. It was also reported that 10 out of 54 cases of LEGH were associated with various types of cellular atypia [13], and coexisting endocervical adenocarcinoma was observed in 19.2% of LEGH [18]. The typical MRI pattern of LEGH is designated as a "cosmos" pattern, although some MDA cases with LEGH were reportedly difficult to distinguish from pure LEGH using preoperative MRI. The prognosis of adenocarcinoma accompanied by LEGH is controversial. Tsuji et al. proposed that the prognosis of adenocarcinoma with LEGH may be favorable [19]. Nishio et al. reported that the mortality rate was approximately 23% in patients with and without LEGH components within tumors [20]. However, the mortality rate we observed in our study was in agreement with the above report only in stage IB patients. Although all the other patients with GAS received adjuvant chemotherapy after surgery, one patient with LEGH did not receive adjuvant chemotherapy, and disease did not recur in this case. Based on these findings, GAS with LEGH may have better prognosis, because it tends to be diagnosed at an early stage.

It is reported that GAS shows aggressive clinical features and frequently metastasizes to lymph nodes, ovaries, the abdominal cavity, and the omentum, unlike HPV-associated typical adenocarcinomas [21]. In our study, lymph node metastasis was frequently observed in the GAS group. Furthermore, the efficacy of adjuvant chemotherapy of GAS was limited, as all cases were stable or progressive diseases as per RECIST. It is also reported that the aggressive nature of GAS might be due to resistance to chemoradiation therapy, unlike that of HPV-associated cervical cancer [4].

An *HER2* amplification rate of 15–30% has been reported in breast cancer and that of 12.2–20% in stomach cancer [5, 22]. The *HER2* oncogene is a member of human epidermal growth factor family and is associated with cell proliferation, so that amplification of *HER2* was a significant predictor of poor prognosis in patients of breast cancer and gastric cancer [23, 24]. In HER2-positive breast cancer and stomach cancer, treatment with a monoclonal antibody against HER2 has resulted in improved survival rates [5]. In a previous study, HER2-positive status was seen in one patient, and equivocal status was seen in four patients, out of 26 patients with GAS [6]. Combined with our findings, it can be concluded that 5–15% of GAS of the cervix may exhibit *HER2* amplification. Endocervical adenocarcinoma, usual type, were positive for HER2 expression with only 1.8% of the usual type [14]. These findings suggest that the frequency of HER2-positive is higher in GAS compared to endocervical adenocarcinoma, usual type of the uterine cervix. Collectively, HER2 may be an attractive therapeutic target for GAS of the uterine cervix. A limitation of our study is the evaluation criteria of HER2 expression. In this study, we applied the criteria for gastric cancer to GAS, because evaluation criteria for HER2 have not been defined for GAS of the cervix. Further investigation into the applicability of these criteria to GAS of the cervix is required. In our study, the DISH assay results revealed six immunohistochemically equivocal cases, two of which were difficult to evaluate due to over-fixation in formaldehyde. For accurate evaluation of *HER2* amplification by DISH assay, suitable fixation is thus necessary, and improvements to the methodology are indicated, to increase success rate.

Conclusion

Although it is difficult to diagnose GAS from biopsy before surgery, clinical symptoms such as watery discharge and lower abdominal pain, high level of serum CA19-9, and immunohistochemistry (HIK1083 and MUC6 staining) can be helpful. Chemotherapy is not effective for GAS, and surgical resection is a strong treatment option for GAS. Some GAS cases showed *HER2* amplification, and thus treatment with a monoclonal antibody against HER2 may be a novel treatment modality for GAS expressing HER2.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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