



# Gastric type mucinous endocervical adenocarcinoma of the uterine cervix: very rare and interesting case

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Gastric type mucinous endocervical adenocarcinomas of the uterine cervix (GAC) are a newly classified mucinous subtype with morphologically in 2014, WHO. They have a much more aggressiveness and show unusual metastatic patterns compared to usual type endocervical adenocarcinoma. They tend to present at higher stage and even in stage I, they have worse survival. Therefore, differential diagnosis of GAC from the usual type of endocervical adenocarcinoma is very important because they are related to a significant risk of recurrence and decreased 5-year disease-specific survival. Besides, GACs are mostly not associated with human papillomavirus (HPV) infection and p16 immunohistochemistry is also typically negative in GAC that is HPV-unassociated tumor. We report a very rare and interesting case of stage IB1 GAC with negative HPV DNA and p16.

**Keywords:** Adenocarcinoma; Mucinous; Gastric type; Human papillomavirus

## Introduction

Endocervical adenocarcinoma represents approximately 20%–25% of cervical cancers, with increasing incidence in recent years [1-5]. The 2014 World Health Organization (WHO) classification of endocervical adenocarcinoma lists the following types: usual type adenocarcinoma, mucinous carcinoma (gastric, intestinal, signet-ring cell type), villoglandular carcinoma, endometrioid carcinoma, clear cell carcinoma, and others (Table 1). Above all gastric type, as a subtype of mucinous adenocarcinoma shows distinct morphologic features, gastric phenotype and an aggressive clinical course [6,7]. Most mucinous adenocarcinomas are considered to be human papillomavirus (HPV)-associated tumor, but studies have shown that gastric type mucinous endocervical adenocarcinomas of the uterine cervix (GAC) is mostly not related to HPV infection [8,9]. And p16 immunohistochemistry is a very useful marker of HPV-associated cervical carcinomas, but it is also typically negative in GAC that is HPV-unassociated tumors [9]. GAC has been reported to have an aggressive clinical course. The 5-year disease-free survival (DFS) rate of patients with GAC (38%) is substantially lower than that of patients with the usual type adenocarcinoma (74%) [7].

We report a rare and interesting case of stage IB1 GAC with negative HPV DNA and p16. In spite of preoperative evalu-

ations that there were negative local invasion and distant metastasis except cervical mass on pelvis magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT), after operation we confirmed parametrial, vaginal, and corpus involvement with pelvic lymph node (LN) metastasis by pathology.

## Case report

A 53-year-old nullipara menopausal woman was referred to our hospital with abnormal Papanicolaou (Pap) smears showing atypical glandular cells in April 2017. She was healthy and had no medical complication but complained of 3 kg

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**Table 1.** 2014 World Health Organization (WHO) classification of glandular tumors of the uterine cervix

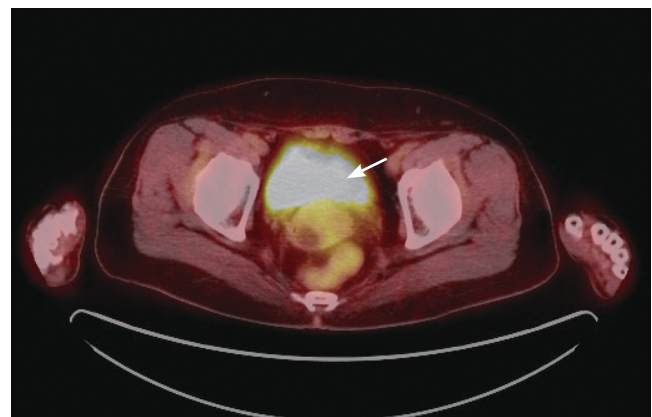
Glandular tumors and precursors
Endocervical adenocarcinoma, usual type
Mucinous carcinoma, NOS
Gastric type
Intestinal type
Signet-ring cell type
Villoglandular carcinoma
Endometrioid carcinoma
Clear cell carcinoma
Serous carcinoma
Mesonephric carcinoma
Adenocarcinoma admixed with neuroendocrine carcinoma

NOS, not otherwise specified.

weight loss for 2 months. She underwent colposcopic exam and followed by punch biopsy and endocervical curettage. Colposcopic finding showed erosive cervix with easy bleeding, but there was no definite acetowhite lesion and vaginal extension. Histological analysis of punch biopsy and endocervical curettage revealed invasive endocervical adenocarcinoma. But, HPV DNA test was negative. Subsequent bimanual rectovaginal examination showed about 2×3×4 cm cervical mass and no parametrial invasion. MRI of the pelvis revealed a longest diameter 3.9 cm sized cervical mass without parametrial and vaginal extension. And there is no evidence of significant LN metastasis and other local invasion in pelvic cavity (Fig. 1). The PET-CT scan showed a heterogenous, moderate fluorodeoxyglucose (FDG) uptake in uterus area which was suspected of malignancy, but there is no significant abnormal FDG uptake to suggest metastatic LN and distant metastasis (Fig. 2). Carbohydrate antigen-125 (CA-125) and carcinoembryonic antigen (CEA) were within normal range, 9.00 U/mL and 1.78 ng/mL, respectively. The results of other examination including sigmoidoscopy, gastroscopy and cystoscopy were unremarkable. In conclusion, the preoperative clinical stage was IB1 according to the International Federation of Gynecology and Obstetrics (FIGO). Therefore, nerve sparing radical hysterectomy (type C1), both salpingo-oophorectomy, bilateral pelvic lymphadenectomy (level 1) and appendectomy were performed at our hospital. After surgery, the pathology revealed that 4×3 cm sized, gastric type mucinous endocervical adenocarcinoma encircling of uterine cervix with 1.4 cm

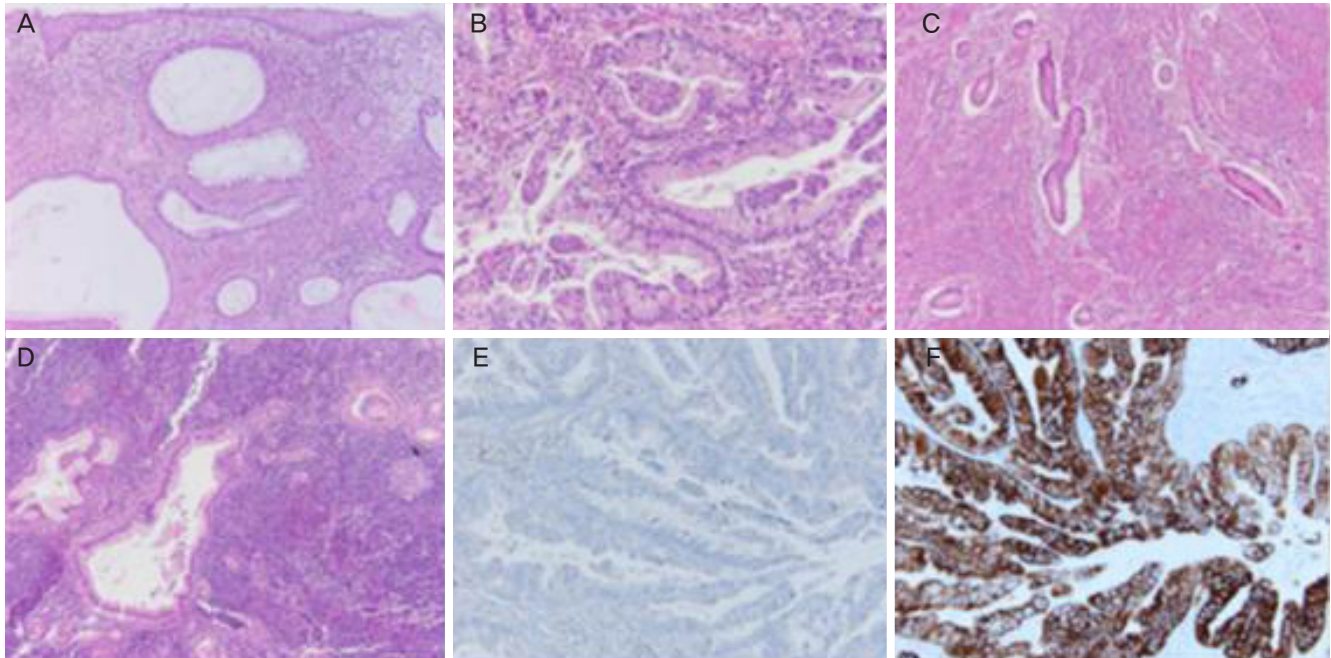


**Fig. 1.** Pelvis magnetic resonance imaging (MRI) revealed a 3.9 cm sized cervical mass without parametrial and vaginal extension.



**Fig. 2.** The positron emission tomography-computed tomography (PET-CT) scan showed a heterogenous, moderate fluorodeoxyglucose (FDG) uptake in uterus area which was suspected of malignancy, but there is no significant abnormal FDG uptake to suggest metastatic lymph node (LN) and distant metastasis.

involvement of 1.5 cm total thickness. And bilateral parametrium, upper two-third of vagina and corpus involvement was present, but surgical margin was all free from everywhere. Metastasis in 3 of 18 regional pelvic LNs and lymphatic invasion were present also. Microscopic examination shows atypical glands extended below the normal level expected for benign endocervical glands. The glands are irregular and



**Fig. 3.** Histologic (A-D; Hematoxylin and Eosin stain) and immunohistochemical (E; p16 stain, F; CK7 stain) findings. (A) Microscopic examination shows atypical glands extended below the normal level expected for benign endocervical glands. The glands are irregular and dilated with gastric differentiation. (B) The tumor shows gastric type differentiation with abundant clear or pale, eosinophilic cytoplasm with atypical nucleus. (C) The tumor invades the myometrium. (D) Tumor cells metastasize to the regional lymph nodes. (E, F) Immunohistochemical stains are negative for p16 (E), positive for CK7 (F).

dilated with gastric differentiation. The tumor shows gastric type differentiation with abundant clear or pale, eosinophilic cytoplasm with atypical nucleus. Immunohistochemical stains are negative for p16, positive for CK7 (Fig. 3). Because of many high-risk factors such as 4 cm size, almost full thickness involvement of the cervix and parametrial, vaginal and corpus involvement with pelvic LN metastasis, she underwent concurrent chemoradiation. She received 6 cycles of weekly cisplatin (40 mg/m<sup>2</sup>) with a total dose of 50.4 Gy pelvic irradiation for 6 weeks.

## Discussion

Endocervical adenocarcinoma shows increasing incidence in recent years [1-5]. By far the most common type of adenocarcinoma is usual type endocervical adenocarcinoma. This is associated with high-risk HPV infection, most commonly HPV types 16 and 18. However, unlike cervical squamous cell carcinoma which nearly all cases are etiologically associated with HPV infection, approximately 10% of endocervical

adenocarcinomas in western countries are unrelated to HPV [10,11]. Therefore, endocervical adenocarcinoma could be classified into HPV-associated and HPV-unassociated groups. The HPV-unassociated group includes gastric, clear cell and mesonephric type [8,9]. Above all, GAC is a rare variant of mucinous adenocarcinoma not associated with HPV infection. And p16 immunohistochemistry is also a very useful marker to distinguish endocervical adenocarcinoma from the benign diseases, but it is typically negative or focal in GAC that is HPV-unassociated group [7]. Not only HPV DNA but also p16 protein are usually positive in the usual type, but are almost negative in GAC with only rare exception [7,8,12]. Our GAC case also shows negative HPV DNA and p16 immunohistochemical stain. In challenging cases, CEA may be a good marker to differentiate these tumors because CEA is usually negative in clear cell carcinoma but increase in GAC [8]. But in our case, CEA was within normal range.

GAC is a clinically aggressive neoplasm with a distinctive histologic appearance. Histologic criteria for GAC were first defined by Kojima et al. to include cells showing clear and/or pale eosinophilic and voluminous cytoplasm with distinct cell

borders comprising the majority of the tumor [7]. GAC represents a distinct, biologically aggressive type of endocervical adenocarcinoma. GAC typically present at a higher stage than HPV-associated group of the usual type. The majority of GAC patients present at advanced stage and pelvic, abdominal, and distant metastases are common. GAC frequently metastasize to ovaries, the abdomen, the omentum, and distant sites. Retrospective reviews of Karamurzin et al. [13] showed that the majority of patients with GAC presented at advanced stage (59% stage II–IV), with only 41% presenting at stage I. In comparison, usual type patients mostly presented at stage I (89%), with only 11% presenting at high stage. GAC had significantly worse disease-specific survival (DSS) than usual type. The 5-year DSS for stage I usual type was excellent at 96%, compared to 62% for stage I GAC [13]. Our case shows bilateral parametrium, upper two-third of vagina and corpus involvement, regional pelvic LNs and lymphatic invasion in spite of preoperative clinical stage IB1.

In conclusion, GAC is more likely to have extracervical involvement and significant decreased 5-year DFS, compared with the usual type [9] Because GAC has significantly worse prognosis and poorer clinical outcomes, the accurate differential diagnosis of GAC from the usual type is very important. And HPV DNA test and p16 immunohistochemical stain are very helpful for differential diagnosis in the cervical adenocarcinoma. When they are negative in the cervical adenocarcinoma, clinicians must consider HPV-unassociated group especially GAC. And we also must keep in mind that both negative HPV DNA test and p16 protein could be a potential pitfall in screening and diagnosis of endocervical adenocarcinoma. Therefore, we must consider more whether the only HPV DNA test is appropriate or not as a screening test for cervical cancer since HPV-unassociated endocervical carcinomas like gastric type are not associated with high-risk HPV infection.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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