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Case Report

Gastric-type mucinous adenocarcinoma of the uterine cervix with neoadjuvant therapy mimicking clear cell carcinoma

Yifen Zhang[1,2], Li Liang[1], Elizabeth D Euscher[1], Jinsong Liu[1*], Preetha Ramalingam[1*]

[1]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [2]Department of Pathology, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, People's Republic of China. [*]Equal contributors.

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Abstract: Gastric-type mucinous adenocarcinoma, an uncommon subtype of cervical carcinoma, is characterized by a distinct morphology and immunophenotype. Herein, we report a case of a 71-year-old woman who received neoadjuvant radiotherapy and chemotherapy after cervical biopsy revealed moderately differentiated invasive endocervical adenocarcinoma. Subsequently, the outside patient underwent radical hysterectomy with bilateral salpingo-oophorectomy. The post-neoadjuvant therapy hysterectomy specimen showed tumor cells with clear cytoplasm, hyperchromatic nuclei with irregular contours, which mimicked clear cell carcinoma. However, immunohistochemical staining showed that these tumor cells were positive for carcinoembryonic antigen, cytokeratin 7 (diffuse), and cytokeratin 20 (patchy), After review of the pretreatment cervical biopsy specimen, the tumor was favored to represent a gastric-type mucinous adenocarcinoma of the cervix. Pathologists should be aware of this rare tumor and its post-neoadjuvant therapy morphologic changes, which can make diagnosis more challenging.

Keywords: Endocervical adenocarcinoma, neoadjuvant therapy, gastric-type, clear cell carcinoma

Introduction

Adenocarcinoma of the uterine cervix, which accounts for 10-25% of all cervical carcinomas, has a wide histopathologic spectrum [1, 2]. The tumor is classified into 7 subtypes: endocervical (usual type), mucinous (gastric, intestinal, signet-ring cell), villoglandular, endometrioid, clear cell, serous, and mesonephric [2]. Mucinous adenocarcinomas of the cervix with gastric-type differentiation include adenoma malignum and gastric-type adenocarcinoma [2]. The latter variant of mucinous carcinoma has distinct morphologic and immunophenotypic features and an aggressive clinical course, hence is considered to be a distinct entity [2, 3]. The diagnosis of gastric-type adenocarcinoma is based on the histological criteria established by Kojima et al.: 1) clear or pale eosinophilic cytoplasm, 2) voluminous cytoplasm, and 3) distinct cell borders [3].

Neoadjuvant chemoradiation followed by radical hysterectomy is one treatment strategy for patients with locally advanced cervical carcinoma [4]. Chemoradiation may change the morphology of the primary tumor. To our knowledge, there are no reports describing the morphologic changes in cervical adenocarcinoma with gastric immunophenotype after neoadjuvant chemoradiation. Herein, we describe a 71-year-old patient with cervical gastric-type mucinous adenocarcinoma who received neoadjuvant chemoradiation followed by radical hysterectomy. Post-neoadjuvant therapy specimen showed morphologic changes that mimicked clear cell carcinoma.

Case report

A 71-year-old woman had a history of Papanicolaou (Pap) smears showing atypical glandular cells of undetermined significance approximately 10 years previously; a Pap smear showing cervical intraepithelial neoplasm-2 and Pap smear showing recurrent atypical glandular cells of undetermined significance 1 year previously. Her most recent Pap smears showed

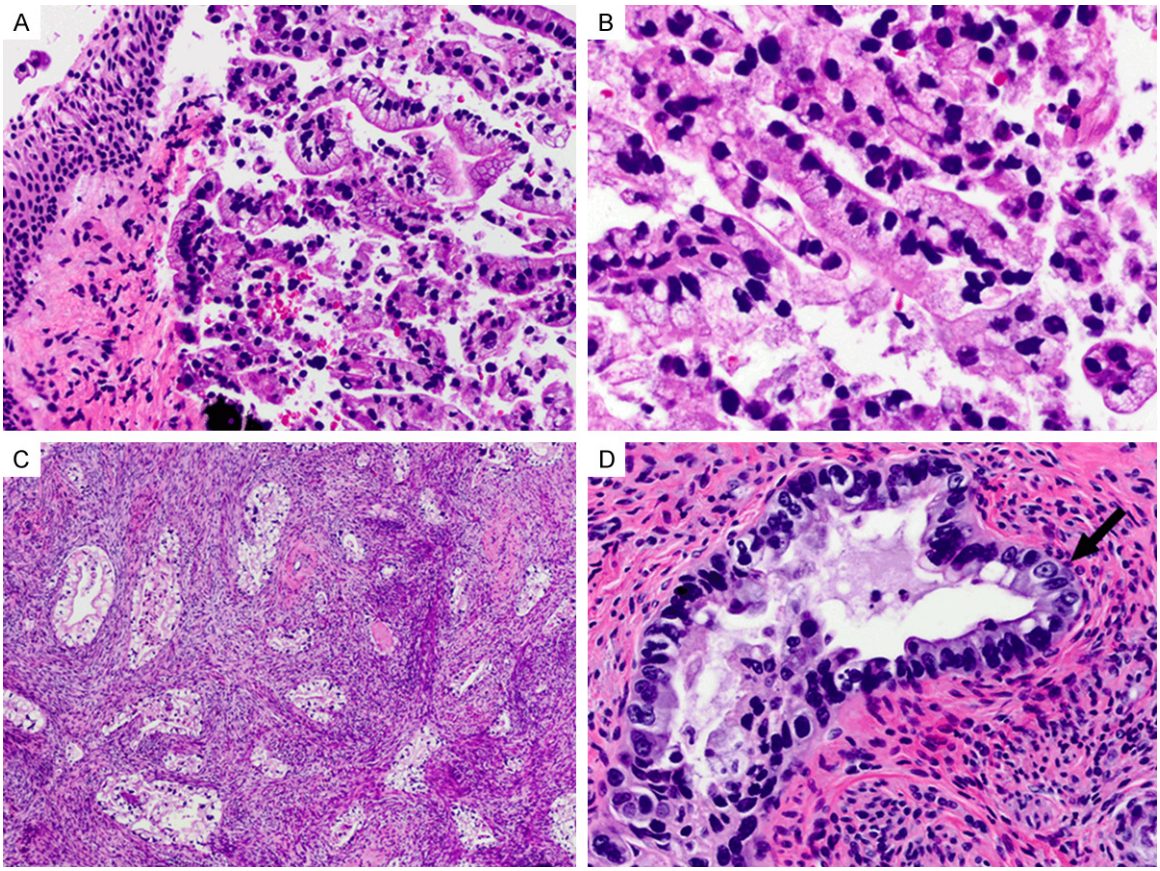

Figure 1. Histopathologic features of gastric-type mucinous adenocarcinoma of the uterine cervix. A: Cervical biopsy specimen obtained before neoadjuvant therapy showing mucinous adenocarcinoma, gastric-type underlying cervical mucosa. B: Cervical biopsy showing well-formed glands and voluminous clear or pale eosinophilic cytoplasm and a distinct cell borders and bland nuclei. C: Radical hysterectomy specimen after neoadjuvant therapy showing infiltrating adenocarcinoma with clear cytoplasm. D: High power showing glands lined with cells with clear to eosinophilic cytoplasm, irregular nuclear contours, with clumping of chromatin and eosinophilic nucleoli, mimicking clear cell carcinoma (arrow). This was consistent with therapy-related changes.

adenocarcinoma. Therefore, she underwent colposcopy and cervical biopsies at an outside institution that was reported as moderately differentiated invasive endocervical adenocarcinoma. Subsequent pelvic examination revealed a bulky cervical mass. Review of outside biopsy material was requested as part of patient work-up. Magnetic resonance imaging of the pelvis revealed a 34 mm × 27 mm × 34 mm cervical mass involving the cervix circumferentially, with parametrial invasion (FIGO stage IIB). Owing to the lesion's full-thickness involvement of the cervix and involvement of the upper vagina, the patient was referred for neoadjuvant chemoradiation prior to surgery. She received only 3 cycles of weekly cisplatin at 40 mg/m^2 before chemotherapy was discontinued secondary to hearing loss. She received concurrent radiation to the pelvis, with a total dose of 43.2 Gy in 24 fractions. She did not receive low-dose-rate intracavitary implants because placing the tandem and ovoid brachytherapy system was not possible. Radical hysterectomy with bilateral salpingo-oophorectomy was then performed at our institution. At this time, review of the outside pre-treatment biopsy was also performed.

Microscopic examination of the pre-neoadjuvant chemoradiation cervical biopsy specimen showed predominantly detached fragments of tumor adjacent to squamous mucosa (**Figure 1A**). The tumor was composed of well-formed glands with clear and foamy to eosinophilic cytoplasm and distinct cell borders. The nuclei were mostly small and basally located without marked pleomorphism (**Figure 1B**). Focal infiltration into the stroma was seen. Immunohistochemical staining with appropriate controls showed the tumor cells were positive for CK7 (diffuse staining) and CK20 (focal) and nega-

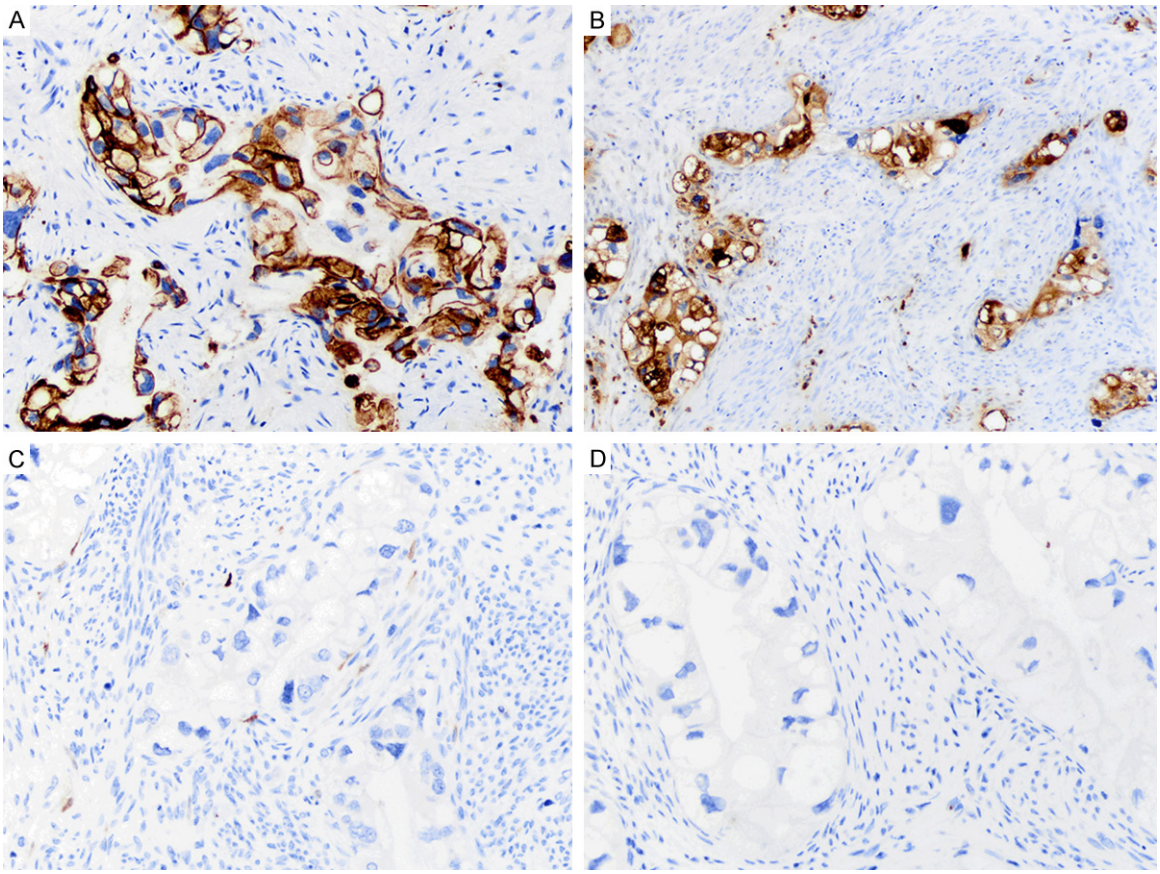

Figure 2. Immunophenotype of gastric-type mucinous adenocarcinoma of the uterine cervix. A: Tumor cells showing diffuse positivity for cytokeratin 7 (CK7). B: Tumor cells sowing diffuse cytoplasmic and membrane staining for monoclonal carcinoembryonic antigen (mCEA). C: Tumor cells showing negative staining for p16. D: Tumor cells showing negative staining for Napsin-A.

tive for estrogen receptor, p16, vimentin, and SMAD4/DPC4. The tumor was not morphologically or immunophenotypically characteristic of typical endocervical adenocarcinoma and a diagnosis of gastric-type mucinous adenocarcinoma of the uterine cervix was favored.

Macroscopic examination of post-neoadjuvant chemoradiation radical hysterectomy specimen showed a residual 2.0 cm × 0.8 cm × 0.5 cm ill-defined firm mass within the endocervical canal involving the endocervix and ectocervix circumferentially. The tumor infiltrated the full thickness of the cervical wall but did not extend into the parametrial or deep margins. The tumor involved the vagina but the margin was negative. Microscopically, the tumor cells infiltrated the cervix stroma and had voluminous clear and pale eosinophilic cytoplasm and distinct borders (**Figure 1C**). Compared to the tumor cells in the biopsy specimen, those in the hysterectomy specimen obtained after chemoradiation showed therapy-related changes, characterized by clearer cytoplasm and larger hyperchromatic nuclei with irregular nuclear contours and prominent nucleoli (**Figure 1D**, arrow). The abundant clear cytoplasm and marked nuclear atypia raised the possibility of clear cell carcinoma. Immunohistochemical staining with appropriate controls showed the tumor cells to be positive for CK7 (**Figure 2A**), CK20 (focal), carcinoembryonic antigen (CEA) (**Figure 2B**) and negative for p16 (**Figure 2C**) Napsin A (**Figure 2D**), estrogen receptor, WT 1, p16, and p53. Concurrent review of the pretreatment biopsy in conjunction with the immunophenotype supported a diagnosis of gastric-type adenocarcinoma with therapy-related changes.

Post-operatively, the patient received four cycles of paclitaxel and carboplatin chemotherapy, but therapy was suspended as she was unable tolerate further treatment. The patient

is alive with disease 15 months after original diagnosis. The most recent computerized tomography scan showed enlarging lesion in the omentum, concerning for recurrent disease.

Discussion

Recent studies have shown that a minority of endocervical-type mucinous adenocarcinomas have a gastric immunophenotype [3, 5, 6]. According to the World Health Organization, gastric-type mucinous adenocarcinomas are a subtype of mucinous carcinoma, with distinct morphologic features, gastric immunophenotype and an aggressive clinical course [2]. This definition is based on the work of Mikami et al [5].

In the past decade, researchers have described a variety of benign, premalignant, and malignant endocervical glandular lesions showing gastric differentiation [5-8]. Benign endocervical glandular lesions include lobular endocervical glandular hyperplasia, simple gastric/pyloric metaplasia, and tunnel clusters (type A); premalignant endocervical glandular lesions include atypical lobular endocervical glandular hyperplasia, and gastric-type adenocarcinoma in situ; malignant endocervical glandular lesions include gastric-type mucinous carcinoma and minimal deviation adenocarcinoma. Among these lesions, minimal deviation adenocarcinoma is considered to be well-differentiated form in the spectrum of gastric-type mucinous carcinoma because it shares the same immunoprofile as gastric-type mucinous carcinoma [9].

Morphologically, gastric-type mucinous carcinoma cells have abundant clear and foamy or pale eosinophilic cytoplasm and distinct cell borders. Their nuclei are enlarged, irregular, and hyperchromatic or vesicular and have eosinophilic nucleoli [2, 6]. The tumor cells form variably-sized simple, angulated, cystic glands, and have some cribriform, solid areas and infolded papillae [2, 6]. The characteristic morphologic features are quite reproducible as shown by Kawakami et al [10]. In this study the degree of diagnostic agreement was comparable to usual type endocervical adenocarcinomas.

Immunophenotypically gastric-type adenocarcinoma of the uterine cervix show neutral mucin production and positive immunohistochemical staining for HIK1083 and MUC6, antibodies positive in pyloric glands of the stomach [5], as well as carcinoembryonic antigen [2, 7]. Most endocervical adenocarcinomas are considered to be Human papillomavirus (HPV)-driven tumors, but studies have shown that gastric-type mucinous carcinomas are mostly unrelated to HPV [11-13]. In our case the tumor was negative for p16, a surrogate marker for HPV-associated tumors. The most important differential diagnosis includes clear cell carcinoma but the latter has features such as hobnail pattern, papillary architecture and stromal hyalinization that are absent in gastric-type cervical adenocarcinoma [3]. Other possibilities though rare include metastatic pancreatic adenocarcinoma that can mimic gastric-type adenocarcinoma. The immunophenotype can show overlap (CK7+, CK20+/-, HPV-) and the diagnosis often is made only with clinical and radiologic correlation. A reportedly specific marker of pancreatic carcinoma is loss of SMAD4/DPC4 that has been used in the distinction of metastatic pancreatic carcinoma from primary ovarian mucinous neoplasms [14]. SMAD4/DPC4 was negative in approximately half of pancreatic adenocarcinoma [15]. Interestingly in our case, SMAD4/DPC4 was negative (with appropriate retained staining in stromal cells), however, the expression of this marker in gastric type adenocarcinoma of the cervix has not been extensively studied and its significance is not certain. In our patient, complete workup showed no pancreaticobiliary excluding the possibility of metastatic pancreatic adenocarcinoma. Earlier studies have reported p53 overexpression in gastric-type adenocarcinoma and minimal-deviation adenocarcinoma [12, 16]. In our case, the tumor was completely negative for p53, consistent with mutated p53 with a null phenotype.

Gastric-type adenocarcinoma has been reported to have an aggressive clinical course. The 5-year disease-free survival rate of patients with gastric-type adenocarcinoma (38%) is substantially lower than that of patients with the usual type of uterine cervical adenocarcinoma (74%) [3]. In the study by Kojima et al., gastric morphology and immunophenotype (HIK1083-positivity) were found to be independent predictive factors of disease recurrence and decreased survival in stage I and II cervical adenocarcinomas [3]. The extremely well-differen-

tiated form of the tumor-minimal deviation adenocarcinoma-also has a less favorable prognosis than the usual type of endocervical adenocarcinoma [2]. The 2-year survival rate of patients with any stage of minimal deviation adenocarcinoma is 20-30%, whereas that of patients with stage I disease is around 50% [13].

In recent years, the use of neoadjuvant chemotherapy and radiotherapy has become an alternative approach for the treatment of cervical cancer, and responsiveness to neoadjuvant therapy before surgery predicts favorable prognosis [17]. Although the effects of neoadjuvant therapy on the histological morphology of other cancers have been well documented, only a few studies have described neoadjuvant therapy-related changes in cancers of the uterine cervix [18, 19]. For instance, Zannoni et al. [19] found that the residual cervical carcinoma cells in the uterine cervix following neoadjuvant radiotherapy and chemotherapy shows a wide pattern of alterations such as cytoplasmic eosinophilia, vacuolation, and foamy appearance; the nuclei are enlarged and irregular and had clumped chromatin and scanty mitotic figures. Multinucleated neoplastic giant cells coexist with reactive foreign body-like giant cells. The stroma is fibrous and contained inflammatory cells, fibrinous debris, cholesterol clefts, hemosiderin pigment, and microcalcifications. In this study, most of the tumors were squamous cell carcinoma; there were only 2 cases of adenocarcinoma.

To our knowledge, the neoadjuvant chemoradiation-related morphologic alterations have not been previously described in gastric-type mucinous carcinoma of the uterine cervix. In the present case, the cytoplasm of residual tumor cells post-neoadjuvant therapy tended to be clearer than that of the cells in the pre-neoadjuvant treatment specimen. Also, the nuclei tended to be more irregular and hyperchromatic with prominent nucleoli. Owing to the abundant clear cytoplasm and atypical nuclei the tumor can mimic clear cell carcinoma. The pre-treatment biopsy was requested and reviewed and the histological similarities in some areas to the post-treatment tumor cells resulted in a diagnosis of gastric-type mucinous adenocarcinoma with therapy-related changes. In challenging cases, CEA may be a good marker to differentiate these two tumors. CEA is usually negative in clear cell carcinoma but positive in gastric-type mucinous adenocarcinoma [13]. Hepatocyte nuclear factor 1-beta (HNF1-β) is expressed in the majority of ovarian clear cell carcinoma but its sensitivity and specificity in uterine and cervical clear cell carcinomas is low [20, 21]. A prior study has shown that HNF1-β was expressed in only 78% of cervical clear cell carcinomas but was also expressed in 40% of usual type cervical carcinomas and 27% of cervical gastric-type adenocarcinoma, limiting its utility in this differential [13]. P16 is a very useful marker of HPV-associated cervical carcinomas, however, they are typically negative in gastric-type adenocarcinomas that are not HPV-related tumors. In conclusion, this case illustrates the morphologic features and special immunoprofile of a rare type of tumor occurring in the uterine cervix. Because neoadjuvant therapy may become more frequently used to treat cervical carcinomas, pathologists should not only keep this uncommon type of tumor in mind but also recognize its therapy-related morphologic alterations.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Jinsong Liu and Preetha Ramalingam, Department of Pathology, Unit 85, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston 77030, TX. Tel: +1-7137451102; Fax: +1-713-563-1848; E-mail: jliu@mdanderson.org (JSL); Tel: +1-7137945659; Fax:+1-713-745-8610; E-mail: PRamalingam@mdanderson.org (PR)

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