

Mini Review

Gastric-type endocervical adenocarcinoma: Review of clinicopathologic characteristics and recent advances

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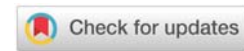
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Abstract

Background: Gastric-type endocervical adenocarcinoma (ECAC) represents a unique variant of endocervical adenocarcinoma that is distinguished by lack of HPV association and an aggressive clinical course with unfavorable prognosis. In this review, we will discuss the clinical and pathologic aspects of gastric-type ECAC, as well as recently described molecular alterations which may be harnessed in future diagnostic and therapeutic strategies.

Results: Clinically, gastric-type ECAC tends to present at an advanced stage with higher rates of extrauterine spread and distant metastasis. Microscopically, gastric-type ECAC is characteristically composed of cells with abundant clear to eosinophilic vacuolated cytoplasm with distinct cell borders, and may demonstrate deceptively benign-appearing morphology. The prognosis of gastric-type ECAC is poor compared to other subtypes of ECAC, as it tends to present with advanced disease and show resistance to conventional chemoradiation therapy. Recent studies have reported a range of molecular alterations in gastric-type ECAC which may have implications in future treatment, including CDKN2A, BRCA2, ERBB2, PIK3CA, ARID1A, and NTRK1/NTRK3 mutations.

Conclusions: Gastric-type ECAC is a relatively recently defined subtype of ECAC with an array of clinical and pathological characteristics that distinguish it from other subtypes of ECAC. As this entity continues to pose difficulties in diagnosis and treatment for pathologists and clinicians alike, continued future investigation is crucial to further our understanding and optimize management of this disease.

Introduction

Gastric-type endocervical adenocarcinoma (ECAC) is a relatively recently characterized subtype of ECAC, defined by its morphologic similarity to gastric pyloric glands and immunophenotypic expression of gastric-type mucin. First recognized and described by Kojima, et al. in 2007, it was added to the WHO classification of tumors in 2014 as a variant of mucinous ECAC, and encompassing Minimal Deviation Adenocarcinoma (MDA) as an extremely well-differentiated form of gastric-type ECAC [1,2]. Recent studies have established gastric-type ECAC as an entity with distinct clinical and pathologic characteristics. Unlike the vast majority of ECACs, gastric-type ECAC is unrelated to high-risk HPV infection [2,3]. Furthermore, in comparison to other ECACs, gastric-type

ECAC is associated with more aggressive clinical behavior and a worse prognosis [1-3]. This review will summarize the clinical and histopathologic features of gastric-type ECAC (Table 1), as well as recent advances in the molecular characterization of these tumors that may significantly impact future directions in diagnosis and treatment.

Clinical features

Gastric-type ECAC has been found to represent the second most common subtype of ECAC after usual-type ECAC, comprising approximately 10% of cases worldwide [4]. Although relatively rare in Western countries, it accounts for up to 25% of cases in Japan [2,4]. The mean age of presentation is approximately 50-55 years (approximately one decade older than patients with usual-type ECAC) [2]. Patients may present

Table 1: Comparison of clinical and histopathologic characteristics of gastric-type versus usual-type adenocarcinoma.

	Gastric-type ECAC	Usual-type ECAC
Etiology	Not associated with high-risk HPV infection	Associated with high-risk HPV infection
Age at presentation	Mean 50-55 years	Mean 40-42 years
Macroscopic appearance	Ill-defined infiltrative mass centered in upper endocervix (may lead to "barrel-shaped cervix")	Often well-defined, exophytic mass arising from transformation zone
Microscopic appearance	Glands lined by cuboidal cells with basally oriented nuclei, abundant clear to eosinophilic cytoplasm, and distinct cell borders	Glands lined by columnar cells with pseudostratified nuclei, abundant apical mitoses and apoptotic bodies
Histologic precursor lesion	Lobular endocervical glandular hyperplasia	Adenocarcinoma in situ
Immunohistochemistry	Negative or focally positive for p16; often mutant-pattern p53 staining; MUC6 and HIK1083 positive	Diffusely positive for p16; wild-type p53 staining

with abnormal bleeding, watery vaginal discharge, abdominal discomfort, or may be asymptomatic [2,5,6]. Cases may also be detected through cervicovaginal cytologic screening, although the sensitivity, particularly in well-differentiated cases, is not high [5,6]. Gastric-type ECAC has a well-documented association with Peutz-Jeghers syndrome, which is caused by a germline mutation in the *STK11* gene on chromosome 19 and also leads to hamartomatous gastrointestinal polyps and increased risk of several types of cancers [2]. Macroscopically, gastric-type ECAC tends to arise from the upper endocervix and form an ill-defined infiltrative mass causing a bulky or "barrel-shaped" cervix (Figure 1), in contrast to usual-type ECAC, which arises from the transformation zone and usually presents as a well-defined mass [7,8]. In addition, gastric-type ECAC often presents at a more advanced stage than other subtypes, with deeper cervical stromal invasion and higher incidence of parametrial and vaginal extension, involvement of other abdominopelvic organs, and metastasis to lymph nodes and distant sites [8,9].

Histopathologic features

Microscopically, gastric-type ECAC is composed of irregularly shaped, small to cystically dilated glands with varying degrees of architectural complexity including intraluminal papillae and occasionally cribriform and solid growth (Figure 2) [5,6,10]. A desmoplastic stromal reaction may be present around the glands at the deep invasive edge of the tumor [5]. The glands are lined by cells that characteristically contain abundant, clear to pale eosinophilic cytoplasm and have well-defined cellular borders [1,3]. The nuclei are typically basally oriented and show low levels of mitotic activity and apoptosis (in contrast to usual-type ECAC, which generally shows nuclear stratification with readily identifiable apical mitoses and apoptotic bodies) [5,10]. The degree of cytologic atypia in gastric-type ECAC can range from mild to marked; MDA represents an extremely well-differentiated form of gastric-type ECAC composed of glands with cytologically bland nuclei and little to no stromal reaction, causing a deceptive morphologic resemblance to benign endocervical glands

[5,8]. In addition, some cases may be seen in association with lobular endocervical gland hyperplasia (LEGH), which appears as a well-demarcated lobular proliferation of small mucinous glands, usually located in the inner half of the endocervical wall (Figure 3) [8,10]. As LEGH often displays gastric-type differentiation and has similar immunophenotypic features and molecular alterations to gastric-type ECAC, it has been hypothesized to represent a precursor lesion to gastric-type ECAC [10-13]. Some cases demonstrate a histologic transition from LEGH to gastric-type ECAC, further supporting this theory [11]. Immunohistochemically, the tumor shows expression of MUC6 (Figure 4) and HIK1083, markers of pyloric-type mucin [2,3,14]. p16 is generally negative or only focally positive, reflecting its HPV-independent pathogenesis [2,14]. Recent studies have shown that up to 50% of cases show a mutant-type pattern of p53 staining (with either diffusely positive or null staining) [2,5,10,14]. PAX8 is positive in 68-88% of cases; although not consistently expressed in gastric-type ECAC, it should be included in the immunohistochemical panel to differentiate these tumors from metastases of gastric adenocarcinomas (which are typically PAX8-negative) [14,15]. In addition, the tumor usually is positive for CK7 and CEA, may be positive for CK20 and CDX2, and is usually negative for ER and PR [13].

Treatment and prognosis

Gastric-type ECAC confers a significantly less favorable prognosis than usual-type ECAC. Patients with gastric-

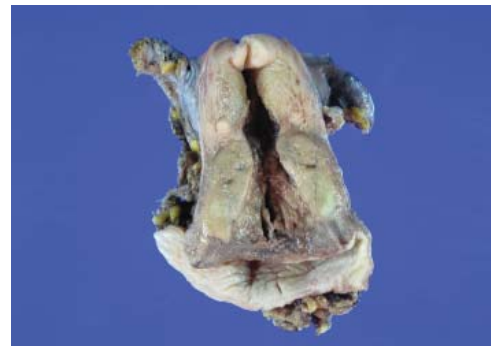


Figure 1: Radical hysterectomy specimen depicting gross features of gastric-type endocervical adenocarcinoma, which often forms an ill-defined infiltrative mass causing cervical wall thickening or "barrel-shaped" cervix.

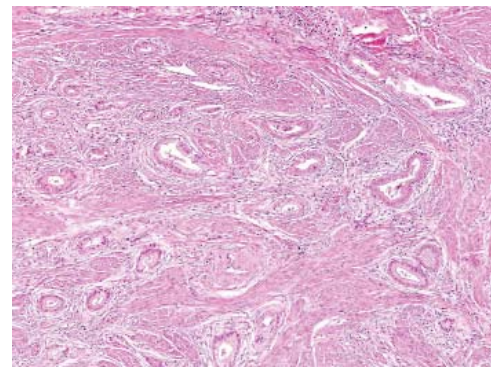


Figure 2: Histologic appearance of gastric-type endocervical adenocarcinoma displaying irregular infiltrative glands composed of cells with abundant foamy cytoplasm, basally oriented nuclei, and distinct cell borders.

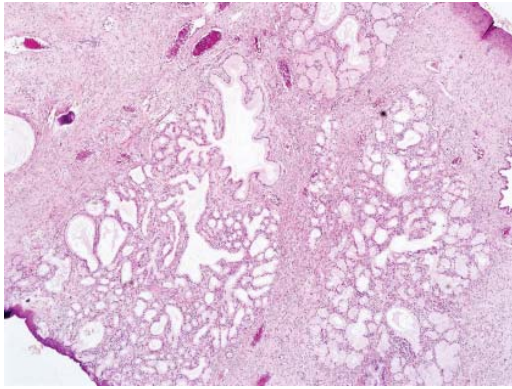


Figure 3: Lobular endocervical gland hyperplasia, characterized by circumscribed lobular proliferation of small glands lined by bland mucinous epithelium with gastric-type differentiation.

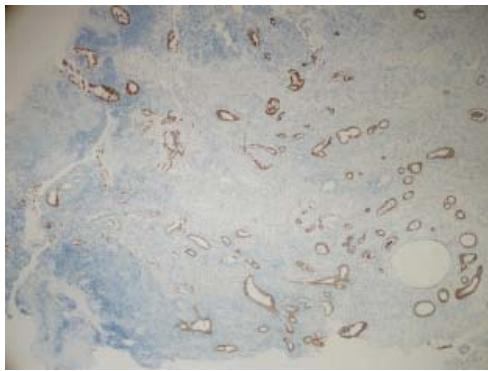


Figure 4: Immunohistochemistry demonstrating MUC6 positivity in gastric-type endocervical adenocarcinoma.

type ECAC tend to present at a higher stage than those with usual-type ECAC; however even when stratifying for stage at presentation, gastric-type ECAC still demonstrates poorer outcomes compared to usual-type ECAC (particularly in early-stage disease) [5,9]. These outcomes include higher rates of lymphovascular invasion, lymph node metastasis, and distant metastasis [5,9]. While gastric-type ECAC shows a propensity to spread to ovaries, abdominal wall/peritoneum, omentum, and urinary tract, other distant sites of metastasis including bowel, liver, lung, bone, and brain have also been documented [8-10]. Patients with gastric-type ECAC also show a higher rate of recurrence with lower progression-free and disease-specific survival (DSS), with Karamurzin, et al. reporting a 42% DSS for gastric-type ECAC compared to 91% for usual-type ECAC [8,9]. Of note, the histologic grade did not affect prognosis, as the survival statistics for cases of MDA did not differ significantly from less differentiated cases of gastric-type ECAC [8]. In addition, patients with gastric-type ECAC display a poorer response rate to chemotherapy and radiotherapy compared to usual-type ECAC [9,16]. In a study of post-neoadjuvant cisplatin and docetaxel-based chemotherapy resection specimens, Kojima, et al. found a 68.8% rate of downstaging upon microscopic examination for usual-type ECAC cases, but a 0% rate for gastric-type ECAC cases [16]. The high rates of chemoresistance and radioresistance in gastric-type ECAC have led investigators to consider alternative molecular-based targeted therapies to potentially achieve better outcomes in

these patients.

Recent advances

Recent studies have examined molecular characteristics of gastric-type ECAC and their potential ramifications in diagnosis and treatment. The most frequent recurrent genetic alterations found include mutations in the TP53 and STK11/LKB1 genes, suggesting that these mutations may play important roles in the pathogenesis of gastric-type ECAC [10,15,17]. Of note, germline STK11 mutations have previously been implicated in Peutz-Jeghers syndrome, and somatic STK11 mutations have been demonstrated in sporadic cases of gastric-type ECAC as well as in the transformation of LEGH to gastric-type ECAC [15,18]. Other alterations found in gastric-type ECAC that may represent actionable mutations for molecular-based targeted therapies include CDKN2A, BRCA2, ERBB2, PIK3CA, ARID1A, and NTRK1/NTRK3 [10,15,17,20]. Garg, et al. also found in their cohort frequent POLE mutations, which have been recently investigated as predictive markers for positive response to immune checkpoint inhibitor therapy [16]. In addition, Jung, et al. and Garg, et al. demonstrated MDM2 amplification in a subset of gastric-type ECAC; as this alteration is currently used to facilitate diagnosis of well-differentiated and dedifferentiated liposarcomas, it may potentially be used in a similar capacity for the identification of gastric-type ECAC cases [10,15].

Conclusions

In conclusion, gastric-type ECAC is a distinctive subtype of ECAC that is not associated with HPV infection and displays an aggressive clinical course with worse outcomes compared to other types of ECACs. Due to its relative rarity in Western countries, HPV and p16 negativity, and potentially bland morphology, this tumor poses diagnostic difficulties and is often under-recognized [6]. In addition, specific treatment options and guidelines for gastric-type ECAC are not well established [9]. However, in the era of widespread HPV immunization, the proportion of non-HPV-associated cervical cancers including gastric-type ECAC may increase in the near future. Therefore, early and efficient detection of these cases by pathologists and optimization of therapeutic modalities by clinicians is critical. To this end, continued clinical, histopathologic and molecular characterization of gastric-type ECAC will further advance our understanding of this entity and future implications in its diagnosis and treatment.

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