# ENDOMETRIAL GASTRIC-TYPE ADENOCARCINOMA ARISING IN THE BACKGROUND OF MUCINOUS METAPLASIA: A CASE REPORT

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**Abstract**

Endometrial gastric-type adenocarcinoma was recently included in the WHO Classification of Female Genital Tumors, 5th edition, as a very rare tumor. Some cases are linked to mucinous metaplasia, and histologic grade does not correlate with prognosis. Currently, there is no standard treatment available. This report describes a 70-year-old female patient who presented with leukorrhea. An endometrial biopsy revealed atypical mucinous glands and a positive result of p16, initially diagnosed as cervical adenocarcinoma. However, after a hysterectomy, a polypoid mass was identified in the endometrial cavity, leading to a revised diagnosis of endometrial gastric-type adenocarcinoma associated with mucinous metaplasia. Immunohistochemical staining showed positive results for CK20, CDX2, and MUC6 in the mucinous metaplasia region, whereas MUC6 was negative in the adenocarcinoma. The tumor was confined to the endometrium with no invasion or spread to lymph nodes. One-year postoperative follow-up showed no recurrence. This cancer is rare and has histological features that overlap with other tumors, underscoring the importance of differential diagnosis for accurate identification.

**Keywords:** endometrial gastric-type adenocarcinoma, endometrial gastric (gastrointestinal)-type mucinous lesion

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## Introduction

Endometrial gastric-type mucinous lesions are rare HPV-independent lesions that have been reported in a limited number of cases. They are morphologically and immunohistochemically similar to their endocervical counterparts, exhibiting a broad morphologic spectrum that ranges from benign to malignant. Wong et al. proposed a set of terminology and diagnostic criteria to categorize them into three groups: mucinous metaplasia of gastric-type, atypical mucinous proliferation of gastric-type, and endometrial gastric-type adenocarcinoma.[1] Herein, we present a case of endometrial gastric-type adenocarcinoma that was misdiagnosed as HPV-associated endocervical adenocarcinoma on biopsy. We also observed a wide range of morphology, spanning benign gastric-type mucinous metaplasia to adenocarcinoma.

## Case presentation

A 70-year-old female patient presented with vaginal discharge, for which a pap smear was performed and showed adenocarcinoma. Subsequent colposcopy showed an unremarkable ectocervix. Cervical biopsy and endocervical curettage showed no abnormalities, whereas endometrial biopsy showed adenocarcinoma **(Figure 1A)** that was diffusely positive for p16 **(Figure 1B)**; thus, a diagnosis of HPV-associated endocervical adenocarcinoma was rendered. The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy.

Gross examination revealed a 3.0 cm polypoid mass arising in the endometrium with an unremarkable cervix and lower uterine segment. Microscopically, the mass originated from the endometrium and consisted of cleft-like spaces surrounded by lobular proliferation of glands lined with atypical columnar cells. This area comprised a significant component of the mass and resembled lobular endocervical glandular hyperplasia, referred to as atypical mucinous proliferation of gastric type by Wong et al **(Figure 1D)**.[1] Definitive invasion or "adenocarcinoma" – characterized by confluent, complex atypical glandular growth with minimal intervening stroma – was also identified **(Figure 1E).** In addition, scattered infiltrative glands and isolated tumor cells with marked atypia were present **(Figure 1F).** These atypical cells exhibited increased mitotic activity, with no evidence of tumor necrosis. At the base of the polyp, there were a few small clusters of benign gastric-type mucinous glands that lacked cytologic or architectural atypia **(Figure 1C).** The background endometrium showed cystic atrophy with no hyperplasia. Myometrial invasion, lymphovascular invasion, lymph node metastasis, extrauterine involvement, or endocervical involvement was not identified after extensive sampling.

Immunohistochemically, both atypical and malignant components expressed CK7 (diffuse, strong) (**Figure 2A**), CK20 (focal, strong) (**Figure 2B**), CDX2 (**Figure 2C**), and PAX8 (focal, weak) and have block-type staining of p16. MUC6 was positive in the atypical component **(Figure 2D)** but negative in adenocarcinoma **(Figure 2E).** Chromogranin A highlighted Paneth-like neuroendocrine cells **(Figure 2F).** Both ER and PR were negative in the adenocarcinoma, while the atypical component demonstrated focal weak expression of ER. The immunoprofile could not be evaluated in the benign component because they were not present in the deeper sections.

Based on these findings, the diagnosis of endometrial gastric-type adenocarcinoma was rendered. The tumor was confined to the endometrium with no lymph node or distant metastasis and therefore classified as pT1aN0M0 and FIGO 2023 stage IC due to its aggressive histologic subtype. The patient subsequently underwent brachytherapy and had no evidence of disease after one year of follow-up.

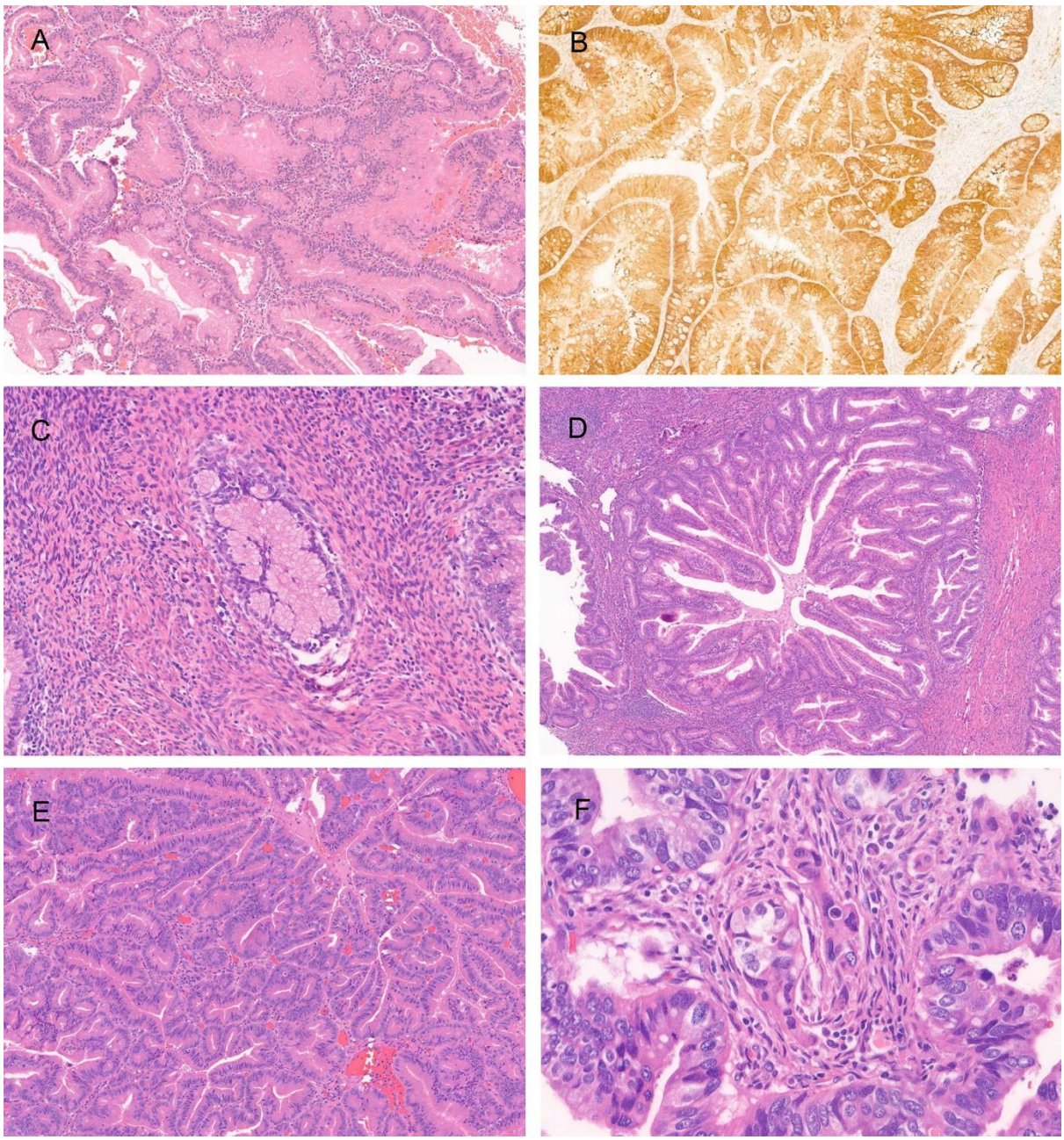


**Figure 1.** Endometrial biopsy demonstrates complex atypical mucinous glands (A) with diffuse, strong p16 expression (B), which led to a misdiagnosis of HPV-associated endocervical adenocarcinoma. The resection specimen shows a spectrum of lesions, including mucinous metaplasia of gastric type (C), atypical mucinous proliferation of gastric type (D), and endometrial gastric-type adenocarcinoma characterized by complex glandular growth (E) and scattered infiltrative glands and isolated tumor cells (F) within the polypoid endometrial mass, without evidence of myometrial invasion.

## Discussion

Endometrial gastric-type adenocarcinoma is a rare tumor, and the true incidence may be underestimated, as it could be misclassified as other types of endometrial carcinoma, such as endometrioid or mucinous carcinoma.[2] Wong et al. evaluated endometrial gastric-type mucinous lesions in nine patients. None of the benign lesions showed block-type p16 staining, while one adenocarcinoma did, where sequencing identified a nonsense mutation in RB1. All benign and malignant lesions expressed CK7 diffusely and at least focal positivity for gastro-intestinal markers (MUC6, CK20, and CDX2). The same group proposed categorizing these mucinous lesions into three distinct groups:

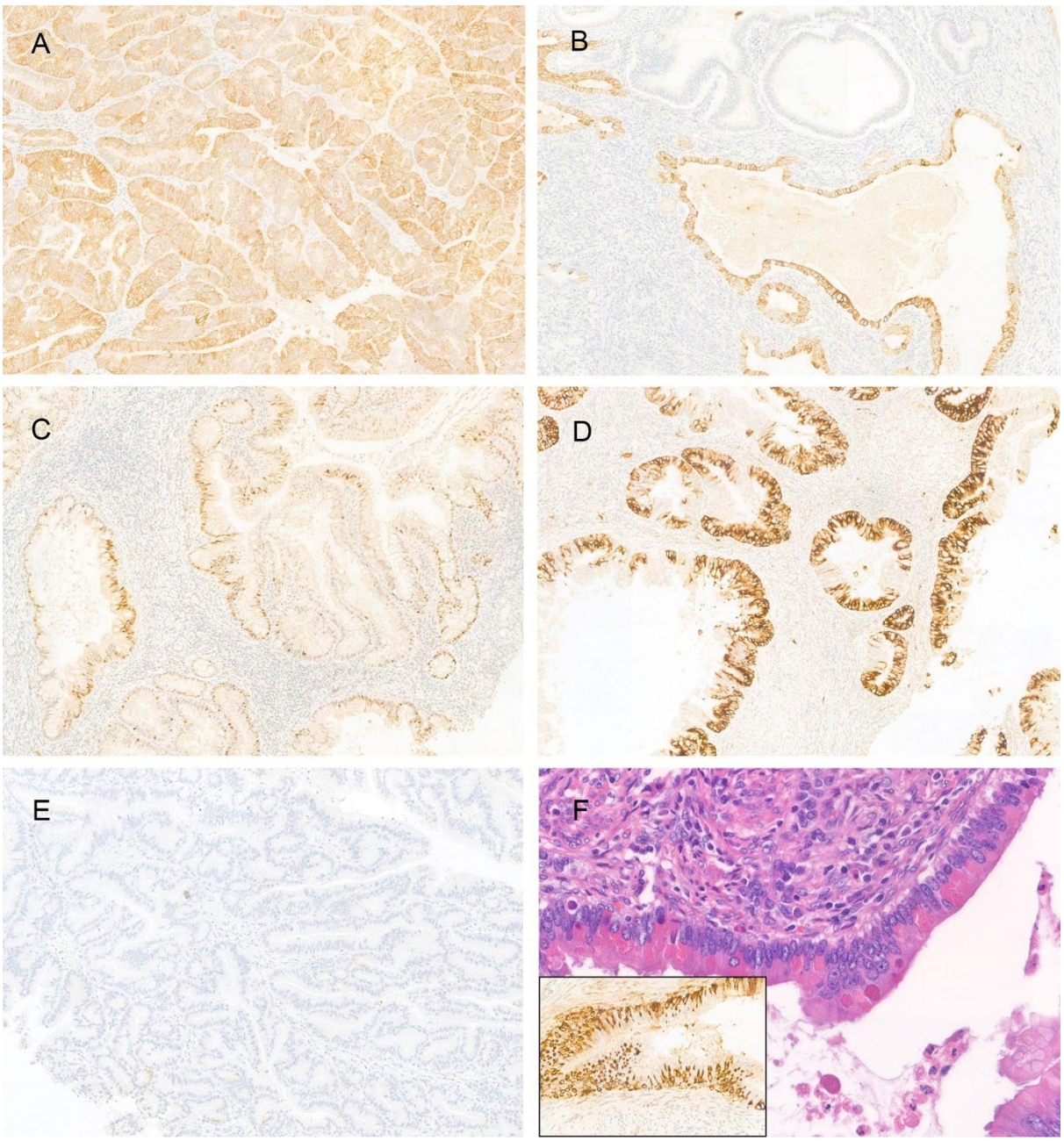


**Figure 2.** These mucinous lesions express gastrointestinal markers, including CK7 (A), CK20 (B), and CDX2 (C). MUC6 stains positively in areas of atypical mucinous proliferation of gastric type (D), while the adenocarcinoma area is negative (E). Paneth-like neuroendocrine cells (F) are highlighted by chromogranin A (insert).

mucinous metaplasia of gastric type, atypical mucinous proliferation of gastric type, and endometrial gastric-type adenocarcinoma.[1] Later, a morphologic spectrum was expanded to include tumors with mild-to-moderate atypia with papillary and glandular formations to high-grade dyscohesive signet ring cells, and the tumor may resemble endometrial serous carcinoma, endometrioid carcinoma, or clear cell carcinoma.[3-4] These lesions can occur alongside synchronous mucinous metaplasia and neoplasia of the female genital tract, with some cases showing an association with Peutz–Jeghers syndrome.[5-6]

Our case exhibited morphology spanning a continuum from benign to atypical and adenocarcinoma, in line with the proposed terminology, and suggests that the benign gastric-type mucinous lesion may have putative premalignant potential. Interestingly, our adenocarcinoma component was negative for MUC6, whereas all

cases of Wong et al.'s were positive.[1] However, their study included only a limited number of endometrial gastric-type adenocarcinoma cases. Larger studies of gastric-type endocervical adenocarcinoma have also reported that these tumors may lack MUC6 expression.[7] Accordingly, our case provides further evidence that endometrial gastric-type adenocarcinoma may also lack MUC6 expression. It is also important to note that distinguishing between benign and atypical lesions, as well as atypical lesions and malignant ones, can be challenging and may lead to poor interobserver agreement, as cytologic atypia and architectural complexity are somewhat subjective, and the lesions can have a continuous nature of morphology

This case highlights a potential diagnostic pitfall, as p16 immunohistochemistry is not a reliable marker for distinguishing between HPV-associated endocervical adenocarcinoma and endometrial gastric-type adenocarcinoma. Moreover, studies of gastric-type endocervical adenocarcinoma have shown that diffuse block-type p16 staining does not necessarily indicate a high-risk HPV-associated adenocarcinoma.[7] The absence of significant apical mitosis and nuclear karyorrhexis should raise consideration of the latter.

## Conclusion

The endometrial gastric-type mucinous lesion presents a morphological spectrum ranging from benign to atypical and malignant. It may possess putative malignant potential, supporting the findings in the previous patient report. This report underscores the importance of recognizing this rare tumor type in differential diagnosis to ensure accurate diagnoses.

**Ethics:** Ethical approval was not required for this type of publication according to institutional guidelines.

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