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Case Report

Gastric (gastrointestinal)-type endometrial adenocarcinoma presenting as a solitary endometrial polyp: a case report and literature review on a novel and potentially aggressive endometrial cancer histotype

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Summary

Gastric-type carcinoma of the endometrium is a rare endometrial cancer histotype, recently introduced in the 2020 WHO classification of the female genital tract tumors. Clinico-pathological features, as well as treatment strategies for this rare histotype, are not fully defined. We herein present an unusual case of endometrial carcinoma with mucinous features arising in a 58-year-old menopausal woman. Morphological features of the present case as well as immunohistochemical profile were consistent with gastrointestinal differentiation. Therefore, after clinical and imaging studies ruled out the possibility of a metastatic origin, a final diagnosis of gastric-type carcinoma of the endometrium was rendered.

Key words: endometrial cancer, gastric-type carcinoma, rare endometrial histotype, differential diagnosis

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Introduction

Primary gastric-type carcinoma of the endometrium (GTEC) is a rare and biologically aggressive endometrial adenocarcinoma showing gastric and intestinal differentiation similar to endocervical gastric-type adenocarcinoma [1]. This entity has been reported in the literature predominantly as case reports or small case series, and therefore its clinical behaviour, diagnostic parameters and treatment strategies are not clearly defined [1-10]. Histological diagnostic criteria have been recently proposed in a small case series [1] and GTEC has been introduced as a novel endometrial cancer histotype in the 2020 WHO classification of female genital tract tumors [11].
We report an additional case of GTEC presenting as a solitary endometrial polypoid lesion in a postmenopausal woman. Clinico-pathological features as well as differential diagnosis and previous literature data on this rare histotype are discussed.

Materials and methods

The present study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical As-

sociation Declaration of Helsinki; all samples were anonymized before histology and immunohistochemistry; therefore, no further ethical approval was necessary to perform the retrospective study.
The non-interventional, retrospective nature of our study did not require any informed consent, even if a written informed consent had been obtained from the patient before surgical procedures. The clinical information was retrieved from medical records and pathology reports. The patients' initials or other personal identifiers did not appear in any image.
Bioptic and surgical specimens were submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques, embedded in paraffin, cut to 5µm and stained with haematoxylin and eosin (H&E). Immunohistochemical studies were performed with the Leica Bond polymer refine detection system using the Leica Bond III automated immunostainer (Leica Medical Systems, Melbourne, Australia, AZ). The antibodies tested were cytokeratin 7 (CK7), cytokeratin 20 (CK20), CDX2, PAX8, p16, p53, estrogen receptor (ER), progesterone receptor (PR) and mismatch repair (MMR) proteins. MMR proteins status was determined with the following antibodies: MSH2 (clone 79H11; Leica), MSH6 (clone EP49; Leica), MLH1 (clone ES05ì; Leica), and PMS2 (clone EP51; leica) in the setting of intact control stromal/lymphocyte staining. Cases were considered as showing stable immunophenotype if any tumor cell nuclei showed positive staining and unstable immunophenotype if all tumor cell nuclei were negative in the presence of internal positive control immunoreactivity. Stromal/lymphocyte staining as well as non-neoplastic endometrial glands served as positive internal controls. p53 immunostaining was assessed according to previously published works regarding staining related to *TP53* mutation [12,13]. Immunostaining for p16 was considered as diffuse if 90% or greater of tumor cells were stained and patchy (non-diffuse) if staining was observed in less than 90% of tumor cells [14].

Case presentation

A 58-year-old menopausal woman presented to our hospital for abnormal vaginal bleeding. Hysteroscopy was performed and revealed a 2 cm polypoid mass located in the right lateral uterine wall, which was resected and submitted for histological evaluation. Patient's past medical history included appendicectomy for an acute appendicitis 10 years before.
Hematoxylin and eosin sections showed a mucinous adenocarcinoma with glandular and solid pattern of growth with necrosis both intra and extra glandular (Fig. 1 A, B). Neoplastic cells showed large, pale eosinophilic or clear cytoplasm with distinct cell borders with variable amounts of intracytoplasmic eosinophilic mucin (Fig. 2 B) and mild to moderate nuclear atypia (Fig. 2 C). The lesion showed a high mitotic rate with atypical mitotic figures.
Immunohistochemical analysis showed diffuse reactivity for CK20, CDX2 and p16, focal positivity for CK7 and PAX8 focally, negativity for estrogen and progesterone receptors and a wild-type p53 pattern. Focal immunoreactivity (< 10%) for chromogranin A and synaptofisin was also observed (Fig. 1 C, D). MLH1, PMS2, MSH2 and MSH6 showed nuclear positivity, so the tumour had a stable immunophenotype.
Diagnosis of high-grade adenocarcinoma with mucinous features, highly suspicious for metastatic origin was initially rendered.
Subsequent clinical workup included ultrasound examination which revealed a superficial, minimal residual endometrial lesion without evident myometrial infiltration or adnexal involvement, esophagogastroduodenoscopy, colonoscopy and imaging studies (PET-and MRI) all of which were unremarkable.
The patient underwent radical hysterectomy with bilateral salpingo-oophorectomy and bilateral sentinel nodes biopsy At gross examination we found an irregular endometrial area located in the right-lateral uterine wall, measuring 1 cm in its largest diameter which showed the same histological and immunophenotypical features of the biopsy. Background endometrium was atrophic without evidence of neoplastic precursor lesions. The depth of myometrial invasion was 3 mm on 10 mm of total thickness.
Lymphovascular space involvement was absent; the cervix, ovaries and fallopian tubes appeared uninvolved. Both bilateral sentinel pelvic lymph nodes had isolated tumour cells (ITC). The peritoneal washing specimen was positive for neoplastic cells.
Based on the described clinical, morphological and immunohistochemical features, a diagnosis of primary endometrial gastric-type adenocarcinoma FIGO stage IA was rendered.
A month after surgery the patient underwent a CT-scan that showed enlarged retroperitoneal lymph-nodes and pelvic-peritoneal localizations of disease. The patient was therefore treated with paclitaxel and carboplatin for 8 cycles and after 6 months treatment showed complete remission of disease.

Discussion

GTEC is a rare endometrial cancer histotype, recently included in the WHO classification of female genital

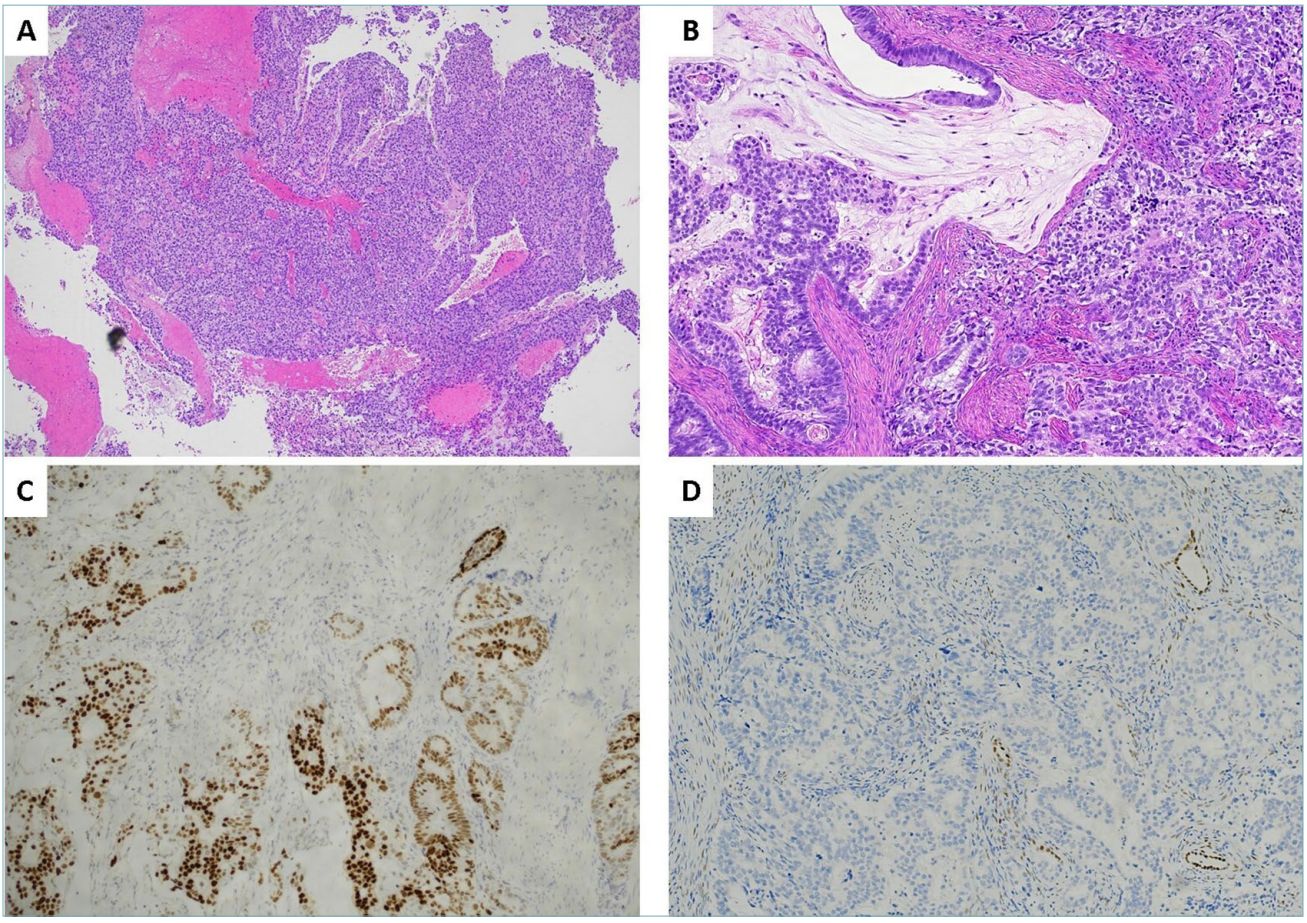

Figure 1. Histological and immunohistochemical findings observed in the biopsy sample. (A) Low power view (x5) showing endometrial bioptic samples diffusely involved by a neoplastic proliferation with solid and glandular pattern of growth. (B) On higher magnification (x10), irregulary shaped, infiltrative mucinous glands were observed. (C) Neoplastic glands showed diffuse staining for CDX2. (D) Estrogen receptors was negative.

tumors [11]. The morphological diagnostic criteria have recently been defined by Wong et al. in their series of 4 cases [1], in keeping with the criteria defined by Kojima et al. [15] for cervical gastric-type adenocarcinoma, including: i) clear or pale eosinophilic cytoplasm, ii) voluminous cytoplasm, iii) distinct cell borders. Additional diagnostic criteria for GTEC are: i) exclusion of cervical involvement, ii) absence of other primary sites, iii) at least focal positivity for one or more gastrointestinal markers (CK20, CDX2, MUC6), vi) focal or absent expression of estrogen and progesterone receptor, v) absence of an endometrioid component [1,15,16].

Since the GTEC histotype was not included in the previous editions of WHO classification of female genital tumors, most endometrial carcinomas with gastric-type morphology could have been incorrectly classified as endometrioid adenocarcinoma with mucinous differentiation explaining thus the lack of large case series on this entity [1-3].

Absence of a typical endometrioid component in CTEC has been considered an essential diagnostic criteria [1-3]. However, a morphologically heterogeneous case of GTEC has been recently reported by Travaglino et al. showing endometrioid, serous, clear cell, mucinous, and gastric-like areas associated with gastric-type metaplasia of the endometrium [3].

The case herein described, along with typical gastric-type morphology showed positive staining for CK20 and CDX2, consistent with gastrointestinal differentiation, while at variance with other reports, we failed to detect mutant p53 staining pattern, GTEC [1-4]. The diffuse (block-type) p16 staining observed in our case is in keeping with the results obtained in 1 of 4 cases of the series reported by Wong et al. [1]. Neuroendocrine differentiation, as highlighted in our case by the posi-

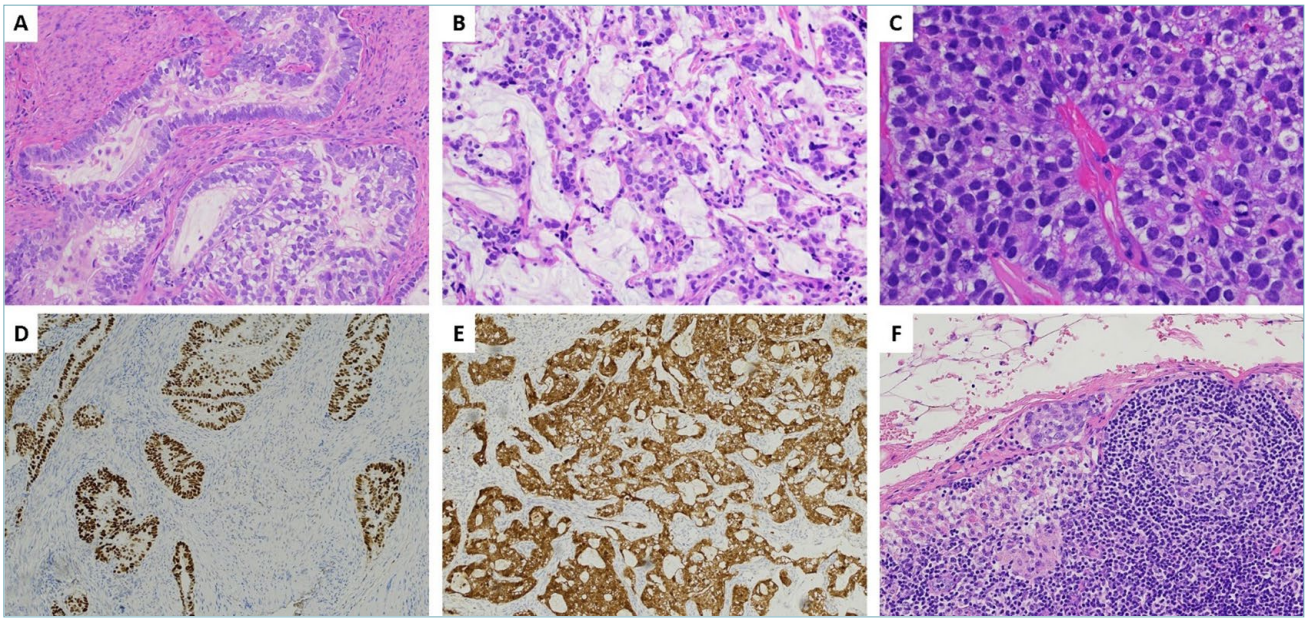

Figure 2. Histological and immunohistochemical findings observed in the surgical specimen. (A) Neoplastic glands were composed of mucinous cells with voluminous clear cytoplasm and distinct cell borders. (B) Neoplastic glands were haphazardly distributed, showed moderate nuclear atypia and variable amounts of intracytoplasmic eosinophilic mucin. (C) Higher magnification (x 20), demonstrating a solid pattern of growth with neoplastic cells showing pale eosinophilic or clear cytoplasm and moderate nuclear atypia. (D) Immunohistochemistry confirmed the diffuse for CDX2 also in the surgical sample. (E) Diffuse staining for p16 was also observed. (F) Microphotograph illustrating isolated tumor cells (ITCs) detected in sentinel lymph-node.

tive stainings for chromagranin A and synaptophysin, has also been observed by Wong at al., who reported scattered chromogranin-positive cells in one case [1,2].

The molecular profile of GTEC is still poorly understood and there are no data regarding the TCGA groups for this histotype.

The main differential diagnoses to rule out before rendering a diagnosis of GTEC are: endometrioid adenocarcinoma with mucinous (Müllerian-type) differentiation, endocervical gastric-type adenocarcinoma, and metastatic origin from the gastro-intestinal tract [16]. Cervical gastric-type adenocarcinoma can be ruled out though a careful and extensive sampling of the uterine cervix to exclude cervical glandular or stromal involvement. Endometrioid carcinoma with mucinous differentiation usually shows areas with typical endometrioid morphology; moreover, mucinous differentiation in these tumors recapitulates the endocervical epithelium rather than the gastric-type mucinous epithelium. Positive immunohistochemical staining for estrogen and progesterone receptors further support the diagnosis of endometrioid histotype.

Finally, the possibility of metastatic origin from gastrointestinal or pancreaticobiliary tract should be always ruled out, especially on biopsy material. In this regard, our case, given the morphological features along with the only focal PAX8 immunoreactivity, was originally considered as possibly metastatic from gastrointestinal primary site. Therefore, a detailed clinical history as well as imaging studies are mandatory to achieve a correct diagnosis.

Our case contributes to expand the knowledge on this rare entity, highlighting that block-type p16 staining as well as neuroendocrine differentiation can be observed in this rare adenocarcinoma histotype. Further studies on larger series are needed to better define the diagnostic criteria as well as molecular background and biological behavior of GTEC.

Conflicts of interest

Authors declare no conflict of interest.

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Authors' contributions

All listed authors contributed to the production of this manuscript and are listed in the appropriate order.

Ethical consideration

None.

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