Letter to Editor

Endometrial adenocarcinoma with gastrointestinal differentiation – a newly described entity, with morphologic diversity

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Gastrointestinal type of endometrial carcinoma is a newly described entity for which clearly defined diagnostic criteria have only recently been published. Among morphologic criteria, gastrointestinal mucinous adenocarcinoma of endometrium must not show a typical endometrioid component. We present a case with morphologic diversity, with areas showing gastric and intestinal differentiation as well as an endometrioid-like component. However, the endometrioid-like component not only did not show classic squamous metaplasia, but was also MUC6-positive, while the positivity for ER/PR was only focal. The recognition of gastric/gastrointestinal differentiation in endometrial carcinomas is best accomplished using both morphology and immunohistochemistry rather than either alone.

Key words: endometrial carcinoma, gastrointestinal differentiation, morphology.

Introduction

Dear Sir,

A 64-year-old patient was admitted to the Gynecology Department due to vaginal bleeding. Ultrasound examination revealed a polypoid uterine lesion of 6 mm diameter and a Pipelle biopsy was recommended. At microscopic examination, atypical glands and villoglandular structures were lined by a mucinous columnar epithelium, being compatible with mucinous adenocarcinoma. Total hysterectomy with bilateral salpingo-oophorectomy was performed and at macroscopic examination, the uterine cavity was filled with a polypoid tumor of 7 mm diameter, surrounded by diffusely thickened endometrial mucosa. Microscopic examination revealed variable architecture of glands and papillae, involving the polypoid tumor as well as in the adjacent endometrium. Most of these structures (80%) were lined by a mucinous columnar epithelium, with abundant clear or eosinophilic cytoplasm, distinct cellular membranes and basally located nuclei, with mild to moderate atypia. Focal intestinal differentiation in the form of goblet cells as well as small non-villous papillae were also identified. Conspicuous neutrophilic infiltrate was present among the neoplastic glands and surrounding stroma while lymphovascular invasion was not present. However, 20% of the tumor glands were lined with stratified atypical cells, with little cytoplasm, suggesting endometrioid differentiation. Immunohistochemical examination showed a similar profile, with tumor cells being positive for MUC6 and p16 as

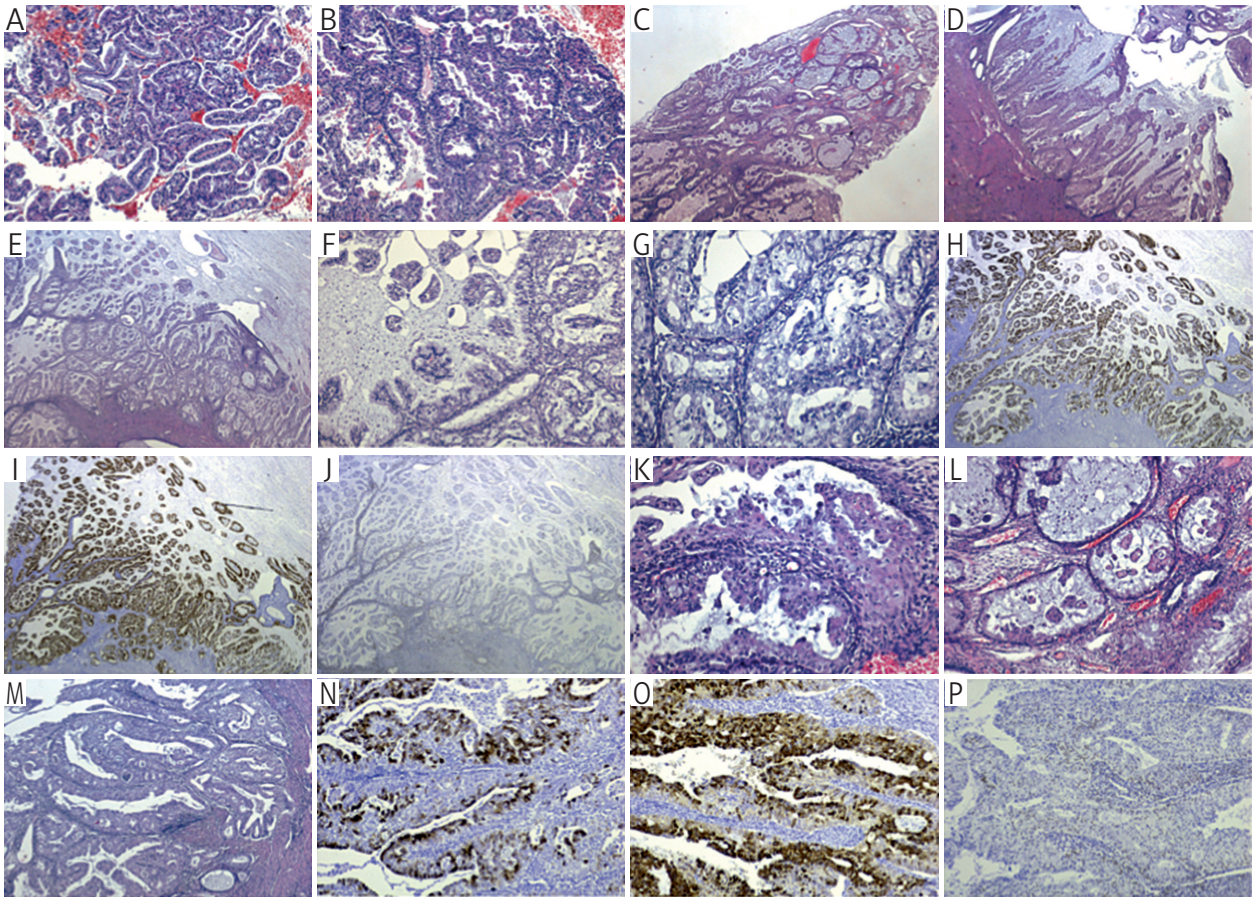

Fig. 1. Microscopic examination of the Pipelle biopsy material revealed atypical glands and villoglandular structures lined with mucinous columnar epithelium (A), focally with small non-villous structures (B); microscopic examination of the hysterectomy specimen identified the polypoid tumor (C) as well as thickened endometrium (D) with glands and papillary structures lined with columnar mucinous epithelium (E) with abundant cytoplasm, welldemarcated cell borders and low (F) to moderately atypical nuclei (G), diffusely positive for MUC 6 (H), block-like for p16 (I) and focally for ER (J); focal intestinal differentiation, areas of cells with eosinophilic cytoplasm (K) and small non-villous papillae (L) were also seen; areas of endometrioid-like morphology (M) were also present, being positive for MUC 6 (N), p16 (patchy) (O) and focally for ER (P)

well as for MSH2, MSH6, MLH1, and PMS2, while ER, PR, and CDX2 were only focally positive and p53 staining was of wild type (Fig. 1). The morphology and immunohistochemical profile are suggestive for an infiltrating endometrial adenocarcinoma of mucinous gastrointestinal type, FIGO grade 2 limited to the endometrium (FIGO stage IA). Isolated case reports of primary gastric or gastrointestinal type of endometrial adenocarcinoma have been published to date [1, 2, 3, 4, 5, 6]. More recently, Wong *et al*. published the largest series of 4 cases, with detailed histologic and immunohistochemical analysis and clearly defined diagnostic criteria [7]. Consequently, the latest WHO 2020 classification incorporated gastrointestinal mucinous adenocarcinoma of endometrium as a distinct entity [8]. The rarity of the tumor may also be due to the fact that in the absence of a specific designation in the previous WHO (2014) classification, this neoplasm was most likely classified as endometrioid adenocarcinoma with mucinous differentiation. Among the well-defined morphologic criteria, gastrointestinal mucinous adenocarcinoma of endometrium must not show a typical endometrioid component. In the present case, the morphology was admixed, with areas showing gastric differentiation (MUC6-positive) and intestinal differentiation (CDX2-positive) as well as an endometrioid-like component and areas presenting with small non-villous papillae. However, the endometrioid-like component not only did not show classic squamous metaplasia, but was also MUC6-positive, while the positivity for ER and PR was only focal. Consequently, the recognition of gastric/gastrointestinal differentiation in endometrial carcinomas is best accomplished using both morphology and immunohistochemistry rather than either alone. When the morphology overlaps with low-grade endometrioid adenocarcinoma, the absence of squamous elements or of significant expression of hormone receptors would support the diagnosis of gastrointestinal mucinous adenocar-

cinoma together with the morphology. Of interest, we have previously reported that besides all human papillomavirus (HPV)-associated mucinous endocervical adenocarcinomas, one third of gastric type HPV-independent endocervical adenocarcinomas may be block-like p16-positive [9]. Also, Wong *et al.* described block-like p16-positivity in one of 4 cases of gastric adenocarcinoma of endometrium. This is an important point to consider when dealing with curettage material, and the differential diagnosis is between gastric type adenocarcinoma with endometrial or endocervical origin versus mucinous HPV-associated endocervical adenocarcinoma, since gastric type endometrial adenocarcinoma can be block-like positive for p16, as in the present case [7, 9, 10]. The importance of differentiating between gastrointestinal and endometrioid type resides in the prognosis and management. Similar to gastric type adenocarcinoma of the cervix and vagina, endometrial adenocarcinomas with gastric differentiation in general exhibit aggressive clinical behavior. In the series by Wong, among the 4 cases, visceral metastases were present in 3, with 2 patients dead of the disease and the other alive with progressive disease [7]. Similarly, both cases reported by Hino *et al.* were advanced at diagnosis and the patients died from the disease, one with lung metastases and the other with peritoneal carcinomatosis [4]. This illustrates the importance of separating these neoplasms from conventional Müllerian type mucinous or endometrioid adenocarcinomas, and they should probably be managed as high-grade neoplasms.

The authors declare no conflict of interest.

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