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Case Report

Papillary mucinous metaplasia: a distinct precursor of mucinous adenocarcinoma of the endometrium

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Abstract: Mucinous adenocarcinoma of the endometrium is heterogeneous, consisting of endometrioid adenocarcinoma composed of >50% mucinous cells, low-grade mucinous adenocarcinoma, microglandular adenocarcinoma, and gastric (gastrointestinal)-type adenocarcinoma. Previous studies have reported that papillary mucinous metaplasia is a possible precancerous lesion of mucinous adenocarcinoma with frequent *KRAS* mutations. Recently, we encountered a case of pure mucinous adenocarcinoma of the endometrium with concurrent papillary mucinous metaplasia in a 35-year-old woman. She underwent 6-month hormonal therapy for atypical endometrial hyperplasia. A follow-up biopsy led to a diagnosis of mucinous adenocarcinoma; therefore, total hysterectomy was performed. The tumor showed abundant intracytoplasmic mucin and mild-to-moderate cytologic atypia with papillary architecture. *KRAS* mutation analysis revealed a point mutation from GGT to GTT in codon 12. Although papillary mucinous metaplasia showed an overexpression of $p16^{INK4}$, especially in the intragrandular papillary tufts, and a low MKi67 labeling index, overt mucinous adenocarcinoma with a loss of $P16^{INK4a}$ expression showed a high proliferating index of MKI67. The mass presented with stage IA disease. During follow-up, the patient was stable and showed no recurrence. Considering the histologic similarity and incidence of *KRAS* mutations between papillary mucinous metaplasia and mucinous adenocarcinoma, papillary mucinous metaplasia may be a precancerous lesion for a subset of mucinous adenocarcinoma of the endometrium.

Keywords: Endometrium, mucinous adenocarcinoma, papillary mucinous proliferation, papillary mucinous metaplasia

Introduction

Mucinous adenocarcinoma of the endometrium accounts for <10% of all endometrial carcinomas [1, 2]. These tumors occur more frequently in postmenopausal or perimenopausal women than in premenopausal women, and >40% of these patients have a history of exogenous hormonal therapy [3]. This is considered a heterogeneous group that consists of endometrioid adenocarcinoma with mucinous differentiation, low-grade mucinous adenocarcinoma, microglandular adenocarcinoma, and gastric (gastrointestinal)-type adenocarcinoma [4-7]. Although some subtypes of mucinous adenocarcinoma have bland cytologic features compared to those of typical endometrioid adenocarcinoma, they have mild-to-moderate architectural complexity. These carcinomas with disparity between cytologic atypia and complex architecture are often difficult to diagnose in curettage specimens. These tumors are well-differentiated, and most patients present at an early stage and have an excellent prognosis [3, 8]. However, in aggressive cases, myometrial invasion, lymphovascular involvement, lymph node or omental metastasis, or cervical stromal invasion are observed in hysterectomy specimens [2]. Some studies have suggested that endometrial mucinous metaplasia strongly correlates with concurrent and subsequent carcinoma [9-11]. In previous studies, papillary mucinous metaplasia was a possible precancerous lesion of mucinous adenocarcinoma with frequent *KRAS* mutations [12, 13]. Recently, we encountered a case of overt mucinous adenocarcinoma of the endometrium in a 35-year-old woman with concurrent papillary mucinous metaplasia. During a review of mucinous proliferative lesions, we suspected that

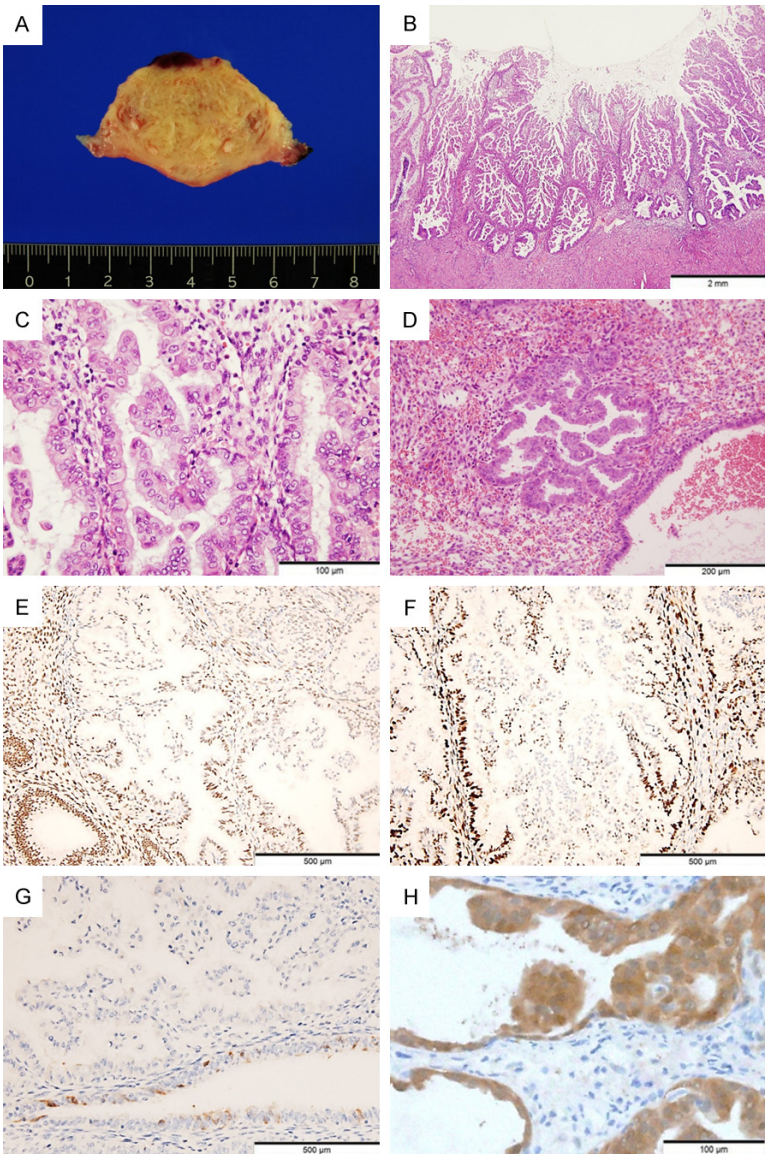

Figure 1. Histopathologic findings of mucinous adenocarcinoma; (A) The tumor is confined to the endometrium. (B) The tumor consists of mucinous epithelial cells showing intraglandular micropapillary growth (×20 objective). (C) The tumor cells display abundant intracytoplasmic mucin, mild-to-moderate nuclear atypia, and no nuclear pleomorphism (×400 objective). (D) Papillary mucinous metaplasia is concurrently located in the adjacent endometrium (×200 objective). (E and F) ER (6F11, 1:100, Novocastra Laboratories, Newcastle, UK) (E) and PR (Clone 16, 1:200; Novocastra Laboratories), (F) immunostains show decreased expression (×100 objective). (G) Loss of $P16^{INK4A}$ (1:10; Pharmingen) expression is noted in overt carcinoma; however, the lower benign endometrial gland shows intervening expression pattern (×100 objective). (H) Papillary mucinous metaplasia shows increased expression of $P16^{INK4A}$ in papillary tufts by immunohistochemistry (×400 objective).

histologic and biologic relationships existed between papillary mucinous metaplasia and low-grade mucinous adenocarcinoma. In an effort to explain the relationship between papillary mucinous metaplasia and mucinous adenocarcinoma, we evaluated the immunohistochemical expression of ER, PR, MKi67, $P16^{INK4A}$, TP53, and PAX2 and analyzed for *KRAS* mutations.

Case presentation

A 35-year-old woman previously presented with abnormal uterine bleeding and undergone curettage 4 years ago. Thus, she was treated with hormonal therapy for atypical endometrial hyperplasia for 6 months at another hospital. At follow-up, ultrasonography showed increased endometrial thickness. Therefore, she was referred to our center for a baseline study. Physical examination revealed no abnormalities. Routine blood tests and urinalysis results revealed normal findings. Pelvic magnetic resonance imaging showed a vague endometrial lesion without myometrial invasion. An endometrial biopsy was performed, and the patient was diagnosed with mucinous adenocarcinoma with micropapillary features. After the diagnosis of intrauterine cancer, the patient underwent total hysterectomy. The resected tumor was located at the superficial endometrium of the left cornu and was a relatively well-circumscribed mass measuring 1.8×1.1×0.8 cm. The cut surface was yellowish-white and soft with hemorrhage. The tumor was confined to the endometrium (**Figure 1A**). On extensive gross examination, other lesions, such as endocervical lesions or lobular endocervical glandular hyperplasia at the cervix, were not identified. The mass presented with stage IA disease. Histologically, the tumor consisted of mucinous epithelial cells showing intraglandular micropapillary growth (**Figure 1B**). The papillary

architecture of this tumor was similar to that of papillary serous carcinoma, but epithelial cells of the tumor showed abundant intracytoplasmic mucin, mild-to-moderate nuclear atypia, and no nuclear pleomorphism (**Figure 1C**). Papillary mucinous metaplasia was also observed in the adjacent endometrium (**Figure 1D**). The expression levels of both ER and PR were decreased in the papillary mucinous lesion compared to those in the surrounding normal endometrium (**Figure 1E** and **1F**). The tumor showed a loss of $P16^{INK4A}$ expression (**Figure 1G**) and no immunoreactivity on TP53 and PAX2 immunostaining. The MKi67 labeling index was <20% of all tumor cells. Immunohistochemistry revealed a reduced expression of PAX2 and PR and an increased expression of $P16^{INK4A}$ in the intraglandular papillary tufts in papillary mucinous metaplasia (**Figure 1H**). Additionally, the patient had a point mutation in the *KRAS* gene from GGT to GTT in codon 12, causing single amino acid substitutions from glycine to valine. The patient was stable and had no recurrence during the follow-up period of 108 months. Written informed consent was obtained from the patient for the present study.

Discussion

Endometrial carcinoma is a heterogeneous group based on clinicopathologic features and molecular pathogenesis. According to the two broad pathogenetic types of Bokhman, type II tumors showing non-endometrioid histology have an aggressive clinical course without a relation to unopposed estrogen stimulation. Precursor lesions of invasive serous carcinomas are known as endometrial intraepithelial carcinomas. In contrast, type I endometrioid cancers are associated with unopposed estrogen exposure and are preceded by premalignant diseases, including endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN) [14]. EIN is a monoclonal proliferation of endometrial cells with multiple genetic mutations preceded endometrioid carcinoma [15]. It is associated with *PAX2* inactivation, *PTEN*, *KRAS*, and *CTNNB1* mutations, and microsatellite instability [16]. Recently, The Cancer Genome Atlas (TCGA) genomic-based classification of endometrial carcinomas proposed four genomic subtypes-hypermutated/microsatellite instability, ultramutated polymerase ϵ mutated, low copy number abnormalities, and high copy number abnormalities [17]. Although the approach proposed by TCGA in clinical practice is useful for predicting the prognosis, standard hematoxylin and eosin staining of a biopsy sample is necessary to diagnose endometrial neoplasia.

Focal mucinous differentiation frequently exhibits in typical endometrioid adenocarcinoma. In practice, mucinous adenocarcinoma is considered a subtype of endometrioid carcinoma with extensive mucinous differentiation (more than 50% of total tumor volume). Pure mucinous adenocarcinoma of the endometrium is a relatively rare disease. In mucinous and microglandular adenocarcinoma of the endometrium, cancerous mucinous epithelia resemble endocervical glands. Nuclear atypia is mild to moderate, and mitotic activity is not prominent [18]. Other rare cases of gastric (gastrointestinal)-type adenocarcinoma have been reported. The tumor displays gastric (or intestinal) morphology with a lobular architecture [7].

Endometrial mucinous and squamous metaplasia have a frequent association with endometrial hyperplasia or carcinoma; thus, it is a diagnostic challenge to differentiate from metaplastic proliferation with architectural complexity and endometrial neoplasia with coexistent simple metaplasia [19]. Complex mucinous proliferations with micropapillary and glandular structures that displayed minimal nuclear atypia in endometrial biopsies should be distinguished from endocervical microglandular hyperplasia and mucinous adenocarcinoma of the cervix or endometrium. In endocervical microglandular hyperplasia, glands show homogeneously microglandular architecture and prominent subnuclear vacuoles with minimal cytologic atypia and mitotic activity. However, endocervical mucinous adenocarcinoma has obvious cytologic atypia, frequent apoptotic bodies, and apical mitotic figures.

In our previous study, we proposed that papillary mucinous metaplasia with complex architecture and minimal cytologic atypia is a precancerous lesion in a subset of endometrial carcinomas with a high frequency of *KRAS* mutations. The intraglandular papillary tufts in papillary mucinous metaplasia showed a reduced expression of PAX2 and PR and an increased expression of $P16^{INK4A}$ on immunohistochemical analysis. However, the prolifera-

tion indices, defined by MKi67, were low [12]. *KRAS*, which encodes a guanine nucleotide binding protein, plays a role in the regulation of cell growth and differentiation by transducing signals from activated transmembrane receptors. *KRAS* and *PTEN* mutations are early events that can be found in hyperplasia and all grades of endometrial carcinomas [20, 21]. *KRAS* mutations are frequent in type I endometrioid carcinomas (10%-30%) [14, 22] and EIN lesions (15%) [15]. In addition, *KRAS* mutations were found in only 2% of uterine serous carcinomas in a previous study [22]. Previous studies have suggested a strong correlation between the mucinous differentiation of neoplastic epithelium and *KRAS* mutations, such as the pancreas (90%), colon (50%), thyroid (50%), lung (30%), and ovary (75%) [23, 24].

Diffuse $P16^{INK4A}$ expression is used as a surrogate marker for high-risk human papillomavirus infection, indicating a uterine cervical origin. However, the induction of $P16^{INK4A}$ in premalignant lesions has been demonstrated in the liver, colon, and pancreas as a cell cycle inhibitor of cell proliferation. Its expression can be linked to oncogene-induced senescence, causing irreversible growth arrest. A previous study of Chekmareva *et al*. demonstrated that $P16^{INK4A}$ expression was useful in distinguishing mucinous and microglandular adenocarcinomas of the endometrium adenocarcinoma from benign endocervical epithelium [18]. In a report by Tsuda *at al*., the expression of $P16^{INK4A}$ and CDK4 may be an early event in the neoplastic transformation of endometrial cancer, and the loss of P16 protein in endometrial hyperplasia may be a precursor to tumorgenensis [25]. Hu *et al.* reported that *p16* hypermethylation was correlated with an increased risk and further progression to endometrial cancer [26]. Although some endometrioid carcinomas may show diffuse $P16^{INK4A}$ expression, the staining patterns are different from those of endocervical adenocarcinoma. The degree of positivity and the intensity of the staining in endometrial endometrioid adenocarcinoma are heterogeneous and less than that of cervical cancer.

In our case, the tumor showed overlapping similarities in nuclear and structural characteristics with papillary mucinous metaplasia. However, overt mucinous adenocarcinoma with a loss of $P16^{INK4a}$ expression displayed a high proliferation index of MKi67. Rarely, papillary mucinous metaplastic lesions located adjacent to endometrioid adenocarcinomas and with expression of $p16^{INK4}$ tend to be inversely correlated with the expression of PR and PAX2; the MKi67 proliferating index is generally low. Although gene alteration test for *CDK2A/P16INK4A* was not performed in our case, the loss of $P16^{INK4a}$ expression was a significant change. The progression of papillary mucinous metaplasia to overt adenocarcinoma needs to be addressed as to further genetic alterations.

In conclusion, papillary mucinous metaplasia may be a precancerous lesion of mucinous adenocarcinoma of the endometrium considering the histological similarity and incidence of *KRAS* mutations between papillary mucinous metaplasia and mucinous adenocarcinoma.

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Disclosure of conflict of interest

None.

Abbreviations

EIN, endometrioid intraepithelial neoplasia; TCGA, The Cancer Genome Atlas.

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