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Clinicopathological Characteristics and *KRAS* Mutation Status of Endometrial Mucinous Metaplasia and Carcinoma

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Abstract. *Background/Aim: Mucinous metaplasia of the endometrium occurs as a spectrum of epithelial alterations ranging from the formation of simple, tubular glands to architecturally complex glandular proliferation with intraglandular papillary projection and cellular tufts. Endometrial mucinous metaplasia often presents a diagnostic challenge in endometrial curettage. Materials and Methods: We analyzed the clinicopathological characteristics and the mutation status for V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) of 11 cases of endometrial mucinous metaplasia. Electronic medical record review and histopathological examination were performed. KRAS mutation status was analyzed using a pyrosequencing technique. Results: Cases were classified histopathologically into simple (5/11) or papillary (6/11) mucinous metaplasias. All (6/6) papillary mucinous metaplasias were associated with atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN; 1/6) or carcinoma (5/6), whereas in a single patient with simple mucinous metaplasia, grade 1 endometrioid carcinoma was incidentally detected. The difference in frequency of association of the metaplasia with AH/EIN or carcinoma was significant (p=0.015). KRAS mutations were identified in five out of six cases of papillary mucinous metaplasias, comprising three cases with G12D and two with G12V mutations; the frequency of KRAS mutation was significantly higher (p=0.015) than in cases of simple mucinous metaplasia (0/5). Conclusion: Papillary mucinous metaplasia is frequently associated with endometrial neoplastic lesions. The high incidence of KRAS mutations in papillary mucinous metaplasia suggests that papillary mucinous metaplasia may be a precancerous lesion of a certain subset of mucinous carcinomas of the endometrium.*

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Endometrial metaplasia is defined as epithelial differentiation that differs from the conventional morphological appearance of the endometrial glandular epithelium (1). Endometrial mucinous metaplasia is particularly relevant as it is frequently encountered in endometrial curettage specimens obtained from peri-menopausal or postmenopausal women (2). Mucinous epithelial lesions of the endometrium present a frequent disparity between cytological atypia and architectural alteration, and often present significant diagnostic challenges to pathologists. Endometrial mucinous metaplasia can occur as a spectrum of alterations ranging from benign-appearing simple mucinous epithelium to malignant-appearing complex epithelial proliferation (1). It is often encountered in hyperestrogenic states or in postmenopausal women receiving hormone replacement therapy (1). Even though endometrial mucinous metaplasia is typically asymptomatic, when associated with endometrial polyps, it may present with menorrhagia, metrorrhagia, dysmenorrhea, and postmenopausal bleeding (3). Endometrial mucinous metaplasia can be also associated with cervical stenosis and may produce mucometra (4). Furthermore, it was recently shown to be associated with concurrent or subsequent endometrial neoplastic lesions (2).

Endometrial endometrioid carcinomas frequently exhibit mucinous differentiation, and a subset of such cases are classified as mucinous carcinomas, when the tumor possesses 50% or more of mucinous components (2). Mucinous carcinoma is an uncommon type of endometrial carcinoma comprising fewer than 10% of endometrial carcinomas, and includes specific variants such as low-grade mucinous carcinoma and microglandular adenocarcinoma (5-10). It has been hypothesized that subtypes of endometrial mucinous metaplasia are pathogenetically related to endometrial carcinoma as possible precursor lesions, and different

morphological classification systems have been proposed to predict the risk of subsequent endometrial carcinoma (4, 11-13). Classification of endometrial mucinous metaplasia into simple and papillary lesion-type based on the presence of intraglandular papillary tufts and complex glandular architecture, was recently proposed (2, 5, 12). Papillary mucinous metaplasia has a high incidence of mutations of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), suggesting that it may be a possible precursor lesion of mucinous carcinoma of the endometrium (2, 5).

To date, only few studies have investigated the clinicopathological and molecular features of mucinous metaplasia of the endometrium. The small numbers of studies regarding endometrial mucinous metaplasia suggest that it is quite a rare entity. In this study, we report our experience with a series of 11 patients who presented with simple or papillary mucinous metaplasia of the endometrium. We herein present a thorough analysis of the clinicopathological characteristics and KRAS mutation status of these cases and a discussion of relevant literature.

Materials and Methods

Case selection. This study (4-2017-0987) was reviewed and approved by the Institutional Review Board at the Severance Hospital (Seoul, Republic of Korea). The cases were extracted from computerized files of the Department of Pathology at the Severance Hospital (Seoul, Republic of Korea). A thorough search of archived surgical pathology cases was performed using the key words "endometrium," "mucinous metaplasia," and "mucinous differentiation". From January 2015 to September 2017, 11 patients were diagnosed as having mucinous metaplasia of the endometrium. The relevant patient electric medical records were reviewed. The clinical profile data including age at the time of diagnosis, menopausal status, coexisting gynecological lesions, association with endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN) or carcinoma, and International Federation of Gynecology and Obstetrics (FIGO) grade (14) and stage (15) of associated endometrial carcinoma were extracted.

Pathological examination. Resected tissues (obtained by gynecological oncology surgeons at the Severance Hospital) were initially examined by pathologists before fixation in 10% neutral-buffered formalin for 12-24 hours. The tissues were then thoroughly examined macroscopically and sectioned. After processing with an automatic tissue processor (Peloris II; Leica Microsystems, Newcastle Upon Tyne, UK), the sections were embedded in paraffin blocks. Four micrometer-thick slices were cut from each formalin-fixed, paraffin-embedded tissue block using a rotary microtome (RM2245; Leica Microsystems), and stained with hematoxylin and eosin using an automatic staining instrument (Ventana Symphony System, Ventana Medical Systems, Tucson, AZ, USA). After staining, a glass coverslip was applied to the slides, which were then submitted to a Board-certified pathologist specializing in gynecological oncology. The pathologist examined the slides by light microscopy (BX43 System Microscope; Olympus, Tokyo, Japan) and issued definite pathological diagnoses. Endometrial mucinous lesions were classified histopathologically as either simple or papillary mucinous metaplasia (5). Simple mucinous metaplasia referred to cases in which simple, tubular-shaped glands were lined by a single layer of columnar, mucin-containing epithelium and had a flat luminal border. In contrast, papillary mucinous metaplasia referred either to cases with intraluminally projecting papillary tufts with or without fibrovascular cores, or to cases with complex or cribriform mucinous glandular architecture without malignant nuclear features. In addition, endometrial hyperplasia was classified according to the 2014 World Health Organization into two groups: hyperplasia without atypia, and AH/EIN (16). Any subsequently available endometrial curettage, resectoscopic endometrial polypectomy, or hysterectomy specimens were obtained and examined histopathologically.

Pyrosequencing. Depending on the size of the tissue sample, genomic deoxyribonucleic acid (DNA) was extracted from six to ten 10-μm-thick formalin-fixed, paraffin-embedded slices using a Maxwell CSC DNA FFPE Kit (Promega Corporation, Madison, WI, USA). The lesions were macrodissected with a scalpel and transferred to 1.5 ml tubes for tissue digestion. The quality and concentration of the extracted DNA was determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Fremont, CA, USA), and adjusted to a concentration of 50 ng/μl. Pyrosequencing analysis of *KRAS* codons 12, 13, and 61 was performed using Therascreen KRAS Pyro Kit (Qiagen, Valencia, CA, USA) according to manufacturer's recommendations. Two nanograms of DNA was used per analysis, and polymerase chain reaction amplification of the target region was performed on a T100 Thermal Cycler (Bio-Rad Laboratories, Hercules, CA, USA). For the pyrosequencing reaction on the PyroMark Q24 System (Qiagen), amplicons were immobilized to the wells of a PyroMark Q24 Plate (Qiagen) using Streptavidin Sepharose High Performance (GE Healthcare Life Sciences, Uppsala, Sweden). Pyrosequencing results were analyzed using PyroMark Q24 Software version 2.0 (Qiagen) with Therascreen *KRAS* Plug-in Report (Qiagen).

Results

Clinical characteristics. Eleven patients with an average age of 53.9 years (range=40-62 years) were included in our study. Table I summarizes the clinical characteristics of 11 patients with endometrial mucinous metaplasia. Nine patients were postmenopausal. The endometrial tissue was obtained from hysterectomies and polypectomies in eight and three patients, respectively. The clinical reasons for hysterectomy included endometrial carcinoma in three, endometrial AH/EIN in one, uterine leiomyoma in one, uterine prolapse in one, cervical high-grade squamous intraepithelial lesion in one (cervical intraepithelial neoplasia 3), and ovarian carcinoma in one. Three patients with endometrial carcinoma underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and paraaortic lymphadenectomy. One patient with ovarian carcinoma underwent total laparoscopic hysterectomy with left salpingo-oophorectomy, peritonectomy, omentectomy, appendectomy, bilateral pelvic lymphadenectomy, and paraaortic lymphadenectomy. The remaining patients

Table I. *Clinicopathological characteristics of endometrial mucinous metaplasia.*

Case no.	Age (years)	Menopause	Type of specimen	Type of endometrial mucinous metaplasia	Association with endometrial AH/EIN or carcinoma				Coexisting gynecological lesion
					Timeline	Type of associated lesion	FIGO grade	FIGO stage (greatest dimension; invasion depth)	
1	47	No	Hysterectomy	Papillary	Concurrent	AH/EIN	-	-	Endometrial extensive tubal metaplasia
2	40	No	Polypectomy	Papillary	Subsequent	Endometrioid carcinoma	Grade 1	Stage IA (0.9 cm; limited to EM; involving adenomyosis)	Endometrial polyp; adenomyosis
3	52	Yes	Hysterectomy	Papillary	Concurrent	Mucinous carcinoma	Grade 1	Stage IA (0.2 cm; limited to EM)	Leiomyoma; cervical endometriosis; left ovarian endometrioid carcinoma; right ovarian endometrioid adenofibroma
4	62	Yes	Hysterectomy	Papillary	Concurrent	Endometrioid carcinoma	Grade 2	Stage IA (1.7 cm; <1/2 of the myometrium; involving adenomyosis)	Leiomyoma; adenomyosis
5	59	Yes	Hysterectomy	Papillary	Concurrent	Mucinous carcinoma	Grade 1	Stage IA (0.2 cm; limited to EM)	Uterine prolapse
6	50	Yes	Hysterectomy	Papillary	Concurrent	Mucinous carcinoma	Grade 1	Stage IA (2.5 cm; <1/2 of the myometrium)	None
7	55	Yes	Hysterectomy	Simple	Concurrent (incidental)	Endometrioid carcinoma	Grade 1	Stage IA (0.3 cm; limited to EM)	Left ovarian endometrioid carcinoma; Right ovarian endometriosis
8	60	Yes	Polypectomy	Simple	No	-	-	-	Endometrial polyp
9	56	Yes	Hysterectomy	Simple	No	-	-	-	Leiomyoma; cervical high-grade squamous intraepithelial lesion
10	57	Yes	Polypectomy	Simple	No	-	-	-	Endometrial polyp
11	55	Yes	Hysterectomy	Simple	No	-	-	-	Leiomyoma

AH/EIN: Atypical hyperplasia/endometrioid intraepithelial neoplasia; EM: endometrium; FIGO: International Federation of Gynecology and Obstetrics.

underwent total laparoscopic hysterectomy in three or total abdominal hysterectomy in one with bilateral salpingo-oophorectomy in three or bilateral salpingectomy in one. Coexisting gynecological lesions included uterine leiomyoma in four, endometrial polyps in three, uterine adenomyosis in two, ovarian endometrioid carcinoma in two, uterine prolapse in one, endometrial extensive tubal metaplasia in one, ovarian endometrioid adenofibroma with mucinous metaplasia in one, ovarian endometriosis in one, and cervical endometriosis with mucinous metaplasia in one.

Two of the patients who underwent polypectomy for simple mucinous metaplasia involving endometrial polyps (cases 8 and 10) developed recurrent endometrial polyps 2 and 10 months after the initial diagnosis of an endometrial polyp. In these cases, the subsequently resected endometrial polyps did not show any evidence of papillary mucinous metaplasia, AH/EIN, or endometrial carcinoma. The remaining patient who underwent polypectomy for papillary mucinous metaplasia involving an endometrial polyp (case 2) underwent total laparoscopic hysterectomy with bilateral salpingectomy for endometrial carcinoma 6 months after the initial diagnosis of the endometrial polyp.

During the follow-up period (range=3-23 months), there were no carcinoma-related mortalities. Currently, all patients remain alive without evidence of disease.

Pathological characteristics. Endometrial mucinous lesions in the 11 cases were classified histopathologically into two

Table II. *V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status of endometrial mucinous metaplasia and carcinoma.*

Simple mucinous metaplasia		Papillary mucinous metaplasia		Carcinoma	
Case no.	*KRAS* mutation status	Case no	*KRAS* mutation status	Case no	*KRAS* mutation status
7	Wild-type	1	Mutant (G12D)	1	Mutant (G12D)
8	Wild-type	2	Wild-type	2	Wild-type
9	Wild-type	3	Mutant (G12V)	3	Mutant (G12V)
10	Wild-type	4	Mutant (G12V)	4	Mutant (G12V)
11	Wild-type	5	Mutant (G12D)	5	Mutant (G12D)
		6	Mutant (G12D)	6	Mutant (G12D)
				7	Wild-type
Total n (%)	0/5 (0.0%)	Total n (%)	5/6 (83.3%)	Total n (%)	5/7 (71.4%)

groups by assessing the extent of mucinous proliferation and the degree of architectural complexity (5, 12) as simple (5/11; cases 7-11) or papillary (6/11; cases 1-6) mucinous metaplasia. Table II summarizes the pathological characteristics of 11 patients with endometrial mucinous metaplasia.

Simple mucinous metaplasia exhibited relatively loose aggregates of variably sized, simple tubular glands lined by a single, uniform layer of mucin-containing, cuboidal, or columnar epithelium (Figure 1A). Most of the glands possessed intraluminal mucin. The luminal surfaces were smooth and flat, without papillary projections. The individual epithelial cells demonstrated no cytological atypia, showed preserved nuclear polarity, and had a uniform nuclear chromatin pattern. The nuclei were round to ovoid, with finely dispersed chromatin and one or two small nucleoli. No nuclear pleomorphism or mitotic figure was identified. In contrast, papillary mucinous metaplasia had a predominantly papillary architecture, which comprised primary and secondary papillae with or without fibrovascular cores and formed intraluminal papillary projections (Figure 1B). Cystically dilated glands possessed floating cellular clusters (Figure 1C), and sometimes exhibited a cribriform-like architecture. In a few areas, intracystic papillary cellular clusters showed nuclear pseudostratification and overlapping (Figure 1D). The majority of individual epithelial cells had a rounded nuclear outline, fine chromatin, and small, conspicuous nucleoli. Even though some epithelial cells exhibited mild nuclear enlargement and a slight irregularity in their nuclear membranes, these features were not associated with an abnormal chromatin pattern or with significant nuclear pleomorphism (Figure 1E). Solid architecture, loss of nuclear polarity, coagulative necrosis, and stromal desmoplasia were absent. Areas of abundant extracellular mucin deposition or mixed inflammatory infiltrates were noted in three out of the six papillary mucinous metaplasia cases (Figure 1F). A single mitotic figure was detected out of the entire lesion in two cases of papillary mucinous metaplasia.

Association of endometrial mucinous metaplasia with AH/EIN or carcinoma. We found that all six papillary mucinous metaplasias were associated with AH/EIN or endometrioid carcinoma. Five out of the six patients with papillary mucinous metaplasia had concurrent endometrial carcinoma (4/5; cases 3-6) or AH/EIN (1/5; case 1). The remaining patient with papillary mucinous metaplasia (case 2) was diagnosed as having grade 1 endometrioid carcinoma involving adenomyosis during a subsequent hysterectomy specimen analysis. In a single patient with simple mucinous metaplasia grade 1 (case 7), endometrioid carcinoma was incidentally detected. Four out of the five patients with simple mucinous metaplasia (cases 8-11) did not develop concurrent or subsequent AH/EIN or carcinoma. The frequency of AH/EIN or carcinoma was significantly higher in patients with papillary mucinous metaplasia than in those with simple mucinous metaplasia (p=0.015). Papillary mucinous metaplasia had a sensitivity of 100.0% (6/6), a specificity of 80.0% (4/5), a positive predictive value of 85.7% (6/7), and a negative predictive value of 100.0% (0/4) for indicating the presence of AH/EIN or carcinoma.

Histologically, the associated endometrial carcinomas were of mucinous type in three and endometrioid in three. Three cases of endometrioid carcinoma displayed a variable degree of mucinous differentiation. Five out of the six cases were FIGO grade 1, and the one remaining case was FIGO grade 2. All cases were FIGO stage IA. The tumor was confined to the endometrium in four cases, whereas in the remaining two cases, the tumor invaded less than half of the myometrium and involved the underlying adenomyotic foci. The greatest dimension of the tumor ranged from 0.2 cm to 2.5 cm (average: 1.0 cm).

KRAS mutation status. KRAS mutation status was analyzed using the pyrosequencing technique. We observed activating *KRAS* mutations in five out of the six cases of papillary mucinous metaplasia (Table II). These comprised three cases with G12D (NM_004985.4:c.35G>A) mutations and two

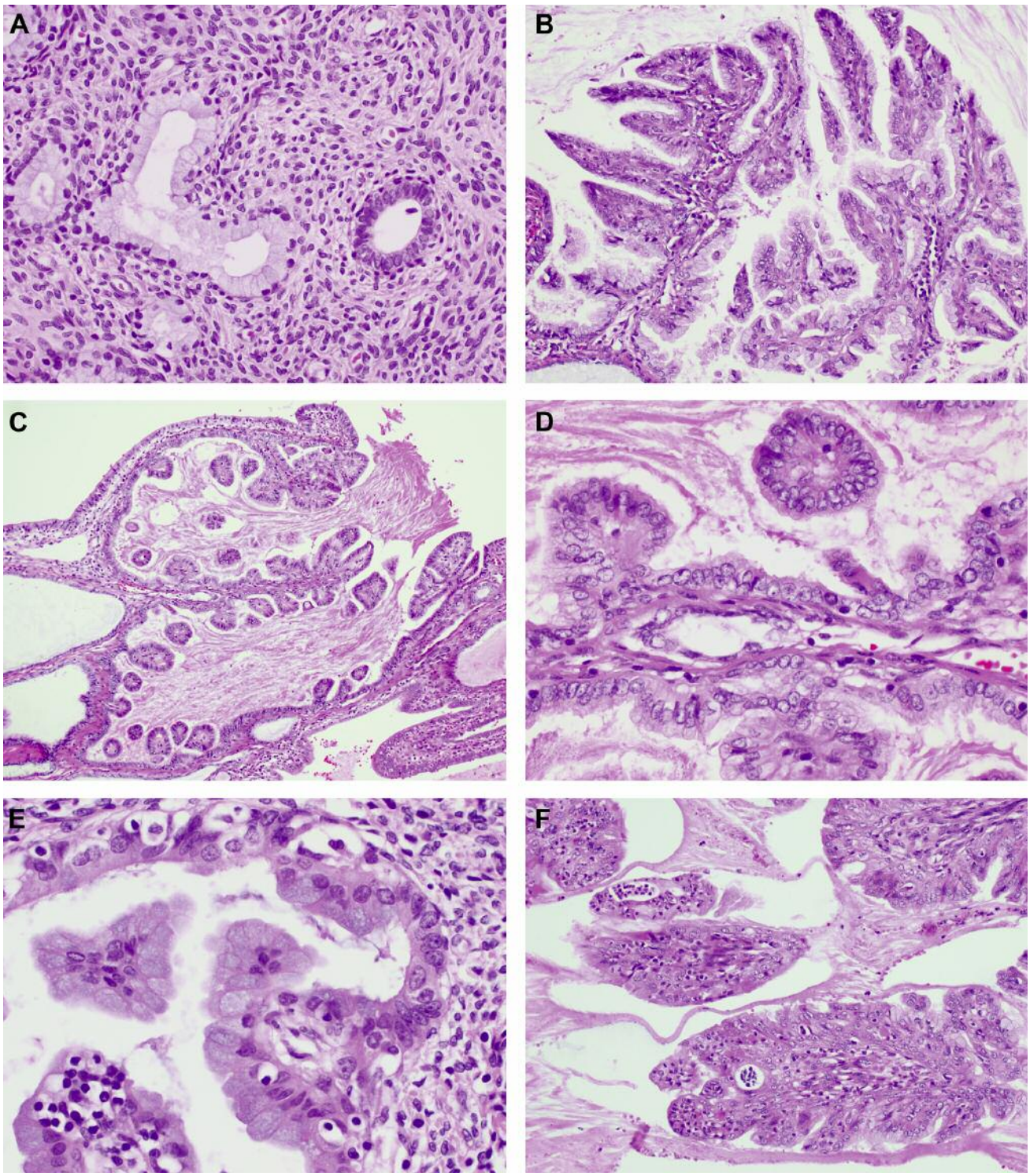

Figure 1. *Histopathological findings of endometrial mucinous metaplasia. A: Simple mucinous metaplasia exhibits small and simple tubular glands lined by a single layer of columnar, mucin-containing epithelium. Their bland nuclei are smaller in size than those of the non-mucinous endometrial glandular epithelium. B: Papillary mucinous metaplasia displays variable degrees of papillation. C: Cystically dilated glands possess prominent intraglandular papillary tufts and extracellular mucin. D: Some papillary cellular clusters show nuclear pseudostratification and overlapping, but obvious cytological atypia is absent. E: The mucinous epithelium of the papillary mucinous metaplasia shows round to ovoid nuclei, finely dispersed chromatin, and one or two conspicuous nucleoli. F: In certain cases, papillae show mixed inflammatory infiltrates, with neutrophils, eosinophils, and lymphocytes. Original magnification: A-B, ×100; C, ×40; D, ×200; E, ×400; F, ×100.*

with G12V (NM_004985.4:c.35G>T) mutations. In contrast, no *KRAS* mutation was observed in simple mucinous metaplasia cases. The frequency of *KRAS* mutations was significantly different between the simple and papillary mucinous metaplasia cases (p=0.015). Of the seven endometrial carcinoma cases, five cases with papillary mucinous metaplasia harbored *KRAS* mutations, which were identical to those observed in the papillary mucinous metaplasia cases.

Discussion

The frequent association and shared common pathways between endometrial metaplastic lesions and neoplasia stress the importance of investigating metaplasia as a potential precursor for endometrial carcinoma (2, 17-19). A significant risk of associated carcinoma in cases with mucinous metaplasia has been reported. In particular, a previous study indicated that endometrial mucinous lesions with complex architectural patterns (*i.e.* papillary mucinous metaplasia) carry the same prognostic significance as conventional AH/EIN (20). It has been suggested that mucinous metaplasia may represent a clonal alteration of the endometrial glandular epithelium (21). Histopathological classifications of mucinous metaplasia using various morphological features have been attempted in the past to predict subsequent risk of developing endometrial carcinoma (12, 13). Lesions with simple architectural patterns of mucinous changes and bland cytological features, in the absence of coexisting precancerous lesions in the nonmucinous epithelium, are usually benign. In contrast, patients with complex architectural patterns of the mucinous epithelium have a significant risk of developing AH/EIN or carcinoma upon follow-up evaluation, with incidence rates ranging from 30.0% to 100.0% (12, 13). In this study, 100.0% (6/6) of patients with papillary mucinous metaplasia presented AH/EIN (1/6) or carcinoma (5/6) in their hysterectomy specimens. This finding is consistent with that of a study by Nucci *et al.* in which the majority of patients with complex mucinous lesions presented endometrial carcinoma in follow-up hysterectomy specimens (12). They classified mucinous epithelial proliferation into three categories: types A, B, and C). Type A proliferation consisted of mucin-containing epithelium, present singly or in small tufts, within architecturally benign glands or involving the endometrial surface. Type B proliferation was more complex, consisting of mucin-containing epithelium, forming small pseudoglands with rigid, punched-out spaces and no supporting stroma. Conspicuous cytological atypia or complex architectural features such as a filiform growth pattern characterized type C proliferation (12). They found the incidence of endometrial carcinoma in follow-up curettages was 0.0%, 64.7%, and 100.0% for types A, B and C, respectively. However, such high incidence of carcinoma associated with endometrial mucinous metaplasia was not observed in other investigations. Alomari *et al.* showed that 42.4% (14/33) of patients with complex mucinous lesions were found to have complex atypical hyperplasia or carcinoma in their follow-up curettage or hysterectomy specimens (2). Yoo *et al.* showed that no progression to overt carcinoma was observed in patients with endometrial mucinous metaplasia (5). The reason for these discrepancies is unclear, but possible explanations include varying histopathological criteria for case inclusion in different studies. For instance, Alomari *et al.* stated that endometrial mucinous lesions with more extensive architectural complexity or severe cytological atypia strongly suggestive of carcinoma were excluded from the complex mucinous category and classified as carcinoma (2).

KRAS mutation is linked to epithelial tumors with mucinous differentiation of various organs including the lung, colon, and the pancreas (2, 22). *KRAS* has also been found to be frequently mutated in mucinous carcinoma of the endometrium (23). More recently, *KRAS* mutations were observed in a high proportion of cohorts of complex, papillary mucinous lesions of the endometrium (2, 5). Alomari *et al.* reported a significantly higher prevalence of *KRAS* mutations in papillary (54.5%) compared to simple mucinous metaplasias (0.0%) (2). Similarly, Yoo *et al.* also showed that 88.9% (8/9) of papillary mucinous metaplasias examined harbored activating *KRAS* mutations, whereas the rate of incidence of *KRAS* mutations in simple mucinous metaplasias was 14.3% (1/7) (5). Consistent with previous data, we observed a significantly higher frequency of *KRAS* mutations in papillary (83.3%; 5/6) compared to simple (0.0%; 0/5) mucinous metaplasias. We also confirmed a high prevalence (5/7; 71.4%) of *KRAS* mutations in endometrial mucinous carcinoma (3/5) or endometrioid carcinoma with mucinous differentiation (2/5), as reported previously (2, 5). Taken together, a high prevalence of *KRAS* mutation in both papillary mucinous metaplasia and endometrial carcinoma suggests a related biological progression and a likely pathological signature that may be applied to mucinous tumors of other organs. However, the existence of *KRAS*-wild-type cases of both papillary mucinous metaplasia and endometrial carcinoma indicates that mutational activation of the *KRAS* gene is implicated in the pathogenesis of a significant subset but not all cases of endometrial carcinoma.

Endometrial mucinous metaplasia and carcinoma often present a diagnostic challenge, particularly in endometrial curettages. The differential diagnosis of simple mucinous metaplasia includes normal mucin-containing endometrial cells, degenerating endometrial glandular epithelium, and contaminant endocervical cells. Firstly, in the absence of other cytological or architectural abnormalities, the presence of a minimal number of endometrial cells with occasional

intracytoplasmic mucin droplets is within the acceptable spectrum of normal. Secondly, intracytoplasmic mucin droplets may also be noted in areas of glandular and stromal breakdown due to anovulation or other dysregulated hormonal conditions. Thirdly, a picket fence-like orderly cell arrangement, basally located squamous metaplastic cells, shorter nuclei, more apically located and lighter cytoplasm compared to that in endometrial cells, are characteristics of normal endocervical cells included in endometrial curettage specimens (1).

Complex, microglandular-like mucinous proliferation observed in papillary mucinous metaplasia should be distinguished from benign and malignant mucinous lesions of the cervix and endometrium: i) A homogeneous architecture, prominent subnuclear vacuoles, minimal cytological atypia and mitotic activity, and reserve cell-like epithelial populations beneath the surface epithelium favor the diagnosis of endocervical microglandular hyperplasia (24, 25). In contrast, luminal squamous metaplasia, stromal foam cells, and the lack of prominent subnuclear vacuoles favor the diagnosis of an mucinous endometrial lesion (26). ii) Immunohistochemical staining for CD10 and CD34 is useful in distinguishing endometrial microglandular adenocarcinoma from benign endocervical glandular epithelium. The endocervical stromal cells demonstrate weak-to-moderate staining for CD10 and strong staining for CD34, whereas endometrial tumors show a reverse pattern (27). iii) Intestinal-type endocervical adenocarcinoma exhibits obvious cytological atypia, including nuclear enlargement, hyperchromasia, abnormal chromatin pattern, increased mitotic activity, and continuous and strong nuclear immunoreactivity (block positivity) for p16 in the neoplastic mucinous epithelium. iv) Mucinous or mixed mucinous and endometrioid carcinomas of the endometrium display a complex architecture with foci of AH/EIN in the adjacent glands (16, 24). v) Metastatic mucinous carcinoma of the stomach or colon consists typically of discohesive signet-ring cells arranged singly or in small clusters, with moderate-to-severe nuclear pleomorphism, mitotic figures, a cribriform architecture, dirty necrosis within glandular lumina, or segmental necrosis of the mucinous epithelium. vi) Low-grade variants of villoglandular adenocarcinoma exhibit a branching architecture with fibrovascular cores lined by pseudostratified endometrioid-type epithelium. These carcinomas may be extremely difficult to distinguish from papillary mucinous metaplasia with villous architecture, in endometrial curettage specimens (1).

In conclusion, we demonstrated that papillary mucinous metaplasia is frequently associated with endometrial neoplastic lesions. The frequency of *KRAS* mutations was significantly higher in papillary mucinous metaplasia. Diagnostic separation of endometrial mucinous metaplasia into morphologically simple and papillary categories constitutes a sensitive, although not specific, approach to predict the risk of AH/EIN or carcinoma of the endometrium. The *KRAS* mutation status offers an additional criterion for highlighting mucinous endometrial lesions that may progress to or coexist with AH/EIN, or carcinoma. The high incidence of *KRAS* mutations in papillary mucinous metaplasia suggests that papillary mucinous metaplasia may be a precancerous lesion of a certain subset of mucinous carcinomas of the endometrium.

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