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Case Report

A case of synchronous mucinous metaplasia and neoplasia of the female genital tract without an STK11 or KRAS mutation ☆

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Introduction

Mucinous lesions of the uterus show marked morphological diversity, including benign, malignant, and non-neoplastic features, and only rarely occur multifocally or involve a wide area of the uterus, even along with fallopian tubes and ovaries (Mangili et al., 2004; Anjarwalla et al., 2007; Zheng et al., 1995; Giles et al., 1994). In these rare cases, making a correct diagnosis is typically challenging because the histological criteria used to differentiate each mucinous lesion are quite arbitrary among pathologists. Mikami et al. (2009) coined the term "synchronous mucinous metaplasia and neoplasia of the female genital tract (SMMN-FGT)" for lesions that were wide-spreading over the mucinous glands. Little information is currently available regarding the somatic genetics associated with SMMN-FGT. We here report a case of SMMN-FGT that was screened for *STK11* and *KRAS* mutations.

Case report

A 52-year-old woman presented at our institution with increased vaginal discharge. She did not have any notable disease history. Peutz–Jeghers syndrome was excluded following a thorough medical examination. Multiple cystic lesions were subsequently detected in the uterine cervix by pelvic CT, and the histopathology of endometrial curettage tissue indicated mucinous adenocarcinoma. Her planned surgery was postponed due to her sudden development of a detached retina, thus one course of paclitaxel–carboplatin chemotherapy was administered for suspected adenocarcinoma then she underwent a total hysterectomy and a bilateral salpingo-oophorectomy. The inner surface of the resected uterus from this patient showed multiple dilated glands with marked mucin secretion (Fig. 1a and b). Histologically, these cystic lesions were composed of a single layer or low-papillary glands of mucinous epithelia. The cystic glands extended widely, replacing the whole endocervical and endometrial mucosa (Fig. 1b and c). Lobular endocervical glandular hyperplasia was also noted; however, neither cytologic atypia nor destructive invasion was observed. Mucinous epithelia were also detected in the glands of adenomyosis without invasive growth pattern (Fig. 1d).

Immunohistochemical analysis revealed that the mucinous glands were diffusely positive for HIK1083 (Fig. 1e), suggesting a gastric phenotype. p53 was negative and Ki-67 positivity was 5.5% in a field of 1000 mucinous cells (Fig. 1f), indicating benign behavior. The epithelia of the bilateral fallopian tubes were intact and no mucinous gland was observed, although the lumens were dilated as a result of mucin congestion. The bilateral ovaries contained neither a mucinous cyst nor a tumor. Peritoneal cytology revealed several mucin-containing epithelial clusters, indicating that the uterine glands had migrated to the peritoneal cavity via the fallopian tubes. To next investigate the somatic genetics of the SMMN-FGT cells, paraffin-embedded tissues were microdissected and DNA was extracted from the mucinous cells and normal squamous cells, respectively. *STK11* is known to be the tumor suppressor gene responsible for the development of Peutz–Jeghers syndrome (Launonen, 2005), and to be involved in sporadic minimal deviation adenocarcinoma of the uterine cervix (Kuragaki et al., 2003). Mutations in KRAS have been reported in 89% of papillary mucinous metaplasias of the endometrial glands, which are potential precursor lesions of endometrial mucinous adenocarcinoma (Yoo et al., 2012). We performed sequencing analysis of the

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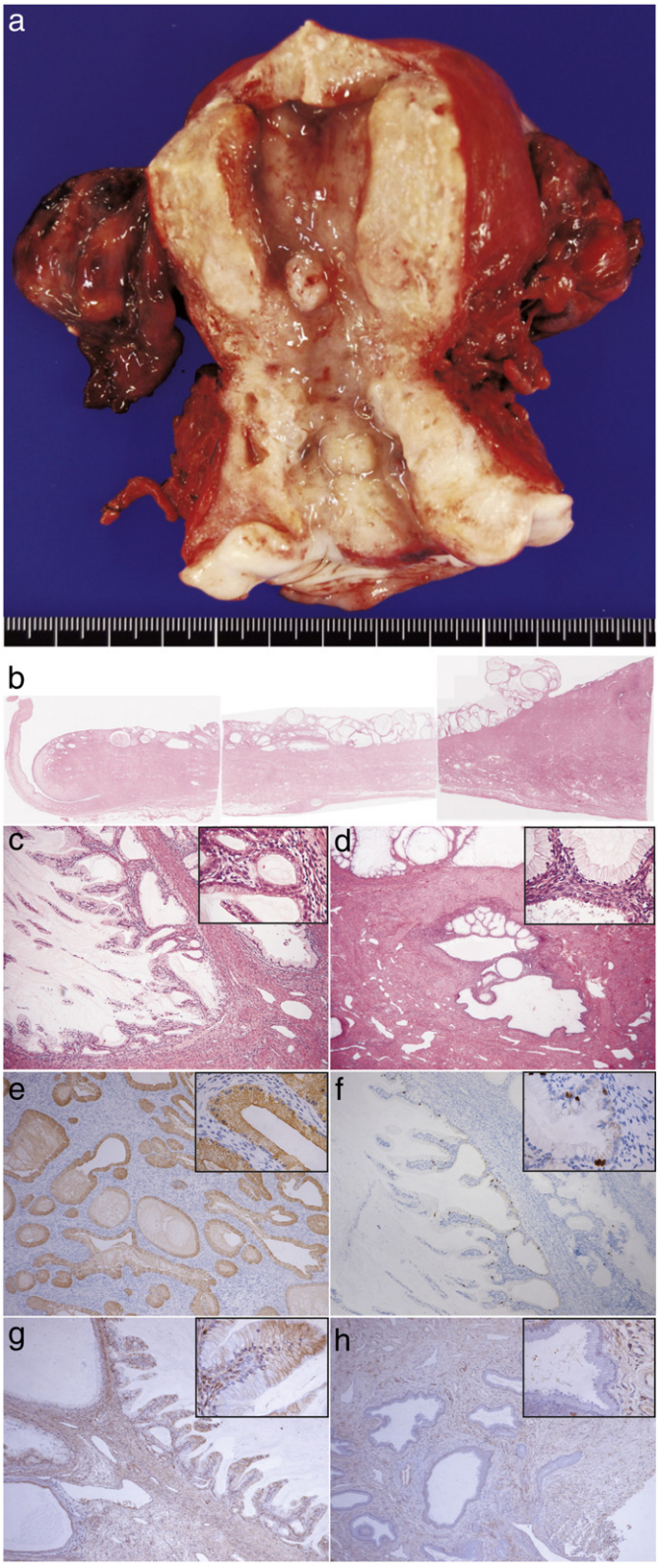

Fig. 1. Pathological findings for the resected uterus in the current patient subject. (a) The surfaces of endometrium and endocervix are filled with mucus secretion. (b) Sagittal section of the lower half of the uterus. (c,d) Photomicrographs of mucinous lesions. Endometrial glands in adenomyosis lesions of the myometrium were found to be replaced by mucinous glands (d). (e–g) Immunohistochemical analyses using HIK-1083 (e), Ki-67 (f), and STK11 (g) antibodies. (h) Immunohistochemistry for STK11 expression using control endocervical tissue from a specimen hysterectomized for uterine leiomyoma. Insets: high power views of the mucinous glands.

STK11 (exons 1–9) and *KRAS* (codons 12, 13, 61) genes in our patient subject. However, the mucinous glands and normal squamous epithelia showed identical sequence patterns, and no mutations were therefore detected. Additional immunohistochemical analysis using anti-STK11 antibody (sc-374300, Santa Cruz Biotechnology, Santa Cruz, USA) revealed that focal positivity in the cytoplasm of mucinous epithelia while no labeling was detected in control endocervical glands of a hysterectomy specimen performed for uterine leiomyomas (Fig. 1g and h), suggesting possible epigenetic activation of STK11 in cases with SMMN-FGT.

Mikami et al. (2009) reported one case died of SMMN-FGT, thus additional five courses of paclitaxel–carboplatin chemotherapy were administered after the surgery.

Discussion

The first report of SMMN-FGT includes two cases with positive results for ascites cytology, and as both of these patients were free from recurrence for more than six months, the authors speculated that positive ascitic cytology would not affect the prognosis (Mikami et al., 2009). In our current case however, histological analysis of the resected tissues did not reveal any overt cytologic atypia or destructive invasion. Hence, mucinous metaplasia or benign neoplasia represented the most plausible etiology. In addition, as the absence of a *KRAS* mutation in the endometrium can indicate a simple mucinous metaplasia (Yoo et al., 2012), a lesion without *STK11* or *KRAS* mutations may be biologically indolent and overtreatment should be avoided. Enhanced STK11 expression in SMMN-FGT would also implicate slow-growing lesion with regulated cell-cycle (Launonen, 2005). Although the positive peritoneal cytology with no preoperative hysteroscopy being performed in our current case suggested intraperitoneal spread of the mucinous glands, we have carefully followed her without further chemotherapy. The pathophysiology of SMMN-FGT is not well understood and classifying these lesions using light microscopy is quite difficult. Long-term and careful follow-up examinations of more cases with SMMN-FGT are needed and more comprehensive further studies, such as DNA sequencing and immunohistochemical analyses of variable cancer-related genes besides STK11 and KRAS, are warranted in these cases to propose diagnostic criteria and elucidate key prognostic factors. This will contribute to establishing an appropriate regimen for each patient with SMMN-FGT.

Conflict of interest statement

None declared.

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