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Case Report

Synchronous mucinous metaplasia and neoplasia of the female genital tract with external urethral meatus neoplasm: A case report

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Introduction

Coexistence of multiple early primary carcinomas in the female genital tract is rare. Mikami et al. coined the term "synchronous mucinous metaplasia and neoplasia of the female genital tract" (SMMN-FGT) for lesions that were widespread over the mucinous glands into the cervix, endometrium, tube, and ovary (Mikami et al., 2009). We herein report a case of SMMN-FGT with external urethral meatus involvement with the analysis of tumor immunohistochemical and molecular profiles.

Case

A 73-year-old nulliparous woman was referred to our hospital with abnormal vaginal discharge and lower abdominal pain. Previous medical history was significant for primary hypertension regulated with medication. Her family history was unremarkable. We visually confirmed the existence of a papillary tumor which had a diameter of about 1.5 cm at the external urethral meatus (Fig. 1). Pelvic examination showed atrophic cervix with large amount of mucinous discharge. Endocervical cytology showed the possibility of mucionous adenocarcinoma. T2-weighted magnetic resonance imaging revealed a uterine cervical canal swelling due to multiple cystic lesions in the canal's full length (Fig. 2a). The endometrial cavity segment was narrowed with the thickness of the endometrium, resulting in hydrometra of the uterine body cavity. The left ovary was enlarged to 88 × 58 mm in size with multiple cystic lesions (Fig. 2b). A polypoid mass was detected at the external urethral meatus. In addition to the MRI findings, computed tomography showed a possibility of small mesenterium dissemination without any lymph node enlargement. Serum tumor markers such as CEA, CA19-9, and CA125 were within normal limits.

Total abdominal simple hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, appendectomy, and mesenteric and external urethral meatus neoplasm resection were performed. The left ovary was enlarged, whereas the right ovary was normal. A few small dissemination less than 1 cm in size were found at the mesenterium with a small amount of ascites (10 ml) cytologically positive for mucinous adenocarcinoma. There were no visually confirmable residual tumors left in her abdomen and pelvis after surgery.

Findings from surgical resection samples were interesting. The cervical canal was enlarged with multiple cervical cystic lesions (Fig. 2c). The most endocervical tumors were arranged in a papillary architecture and replaced preexisting glands with a focal stromal microinvasion (Fig. 2d). The endometrial tumor was diffuse, and a focal stromal invasion cannot be ruled out (Fig. 2e, f). There was no obvious continuity between the endocervical and endometrial lesions (Fig. 3a, b). The ovarian tumor was enlarged to about 10 cm in size and was a multicystic tumor with a solid component (Fig. 3c). Microscopically, this tumor was identical to a mucinous borderline tumor (Fig. 3d). External urethral meatus neoplasm was about 1.5 cm in size (Fig. 3e). All microscopic findings including external urethral meatus neoplasm were similar to the other mucinous lesions such as uterus, ovary, and mesenteric (Fig. 2d, f, 3d, f). On the right adnexal surface and mesentery, there were multiple small foci of implanted mucinous tumor cells. All neoplasms except for mesenchymal lesions were invasive (Table 1). The left fallopian tubes remained basically intact, and the appendix vermiformis was unremarkable.

Using immunohistochemistry (IHC), all tumors except for gastric cancer showed a strikingly similar pattern; each tumor was positive for HIK1083, MUC5AC, MUC6, and HGM, but negative for CDS2 and p16 (Table 1). Only ER in the endometrium and MUC in the urethra were diffusely positive. On the other hand, the result of gastric neoplasia showed positive for CDX2, but negative for HIK1083, MUC5AC, MUC6, and HGM, indicating that the origin was independent from the other tumors. Then, the possibility of *G-nas* (exons 8 and 9) and *KRAS*

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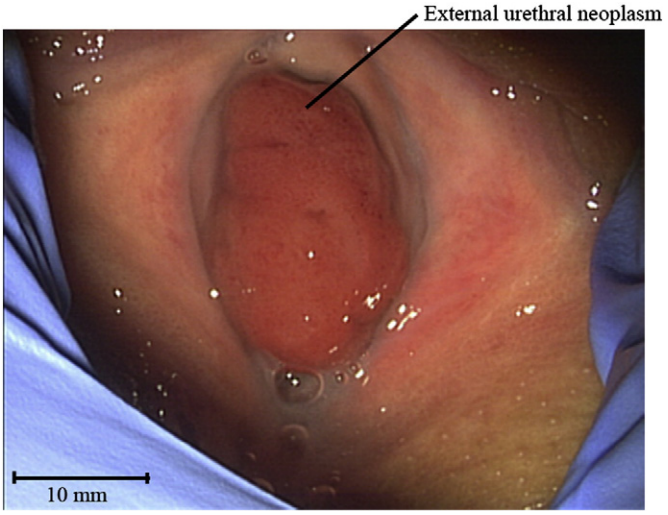

Fig. 1. External urethral tumor about 1.5 cm in size.

(exon 2) mutations in tumors was explored with PCR-direct sequencing according to previous studies (Matsubara et al., 2014), and no mutations were detected. These pathological and molecular findings indicated this disease as a SMMN-FGT with external urethral meatus neoplasm.

Because the existence of multiple invasive neoplasms indicated high possibility of recurrence, 6 cycles of adjuvant chemotherapy with paclitaxel and carboplatin were performed. She then underwent both a gastroscopy and colonoscopy to exclude the possibility of Peutz–Jeghers syndrome (PJS). No polyposis was found in her gastrointestinal tract, however superficial gastric cancer was found at the outlet of the stomach. Later, tumor resection was performed by endoscopic submucosal dissection. Results of IHC in submucosal tumor showed no association with SMMN-FGT. Unfortunately, multiple lung metastases were found 6 months after the last course of chemotherapy.

Discussion

Synchronous multifocal mucinous lesion, termed "synchronous mucinous metaplasia and neoplasia of female genital tract" involving the uterine cervix, corpus, fallopian tubes, and ovaries, is a rare disease (Mikami et al., 2009). The condition demonstrates a spectrum of morphological features ranging from metaplasia to invasive mucinous adenocarcinoma, including minimal deviation adenocarcinoma of the cervix (Mikami et al., 2009). In our case, the cervical tumor was an invasive mucinous adenocarcinoma. However, the other neoplasms were not considered the result of cervical cancer metastasis, because all other neoplasms were metaplasias or borderline tumors. We recognize that our case is not a single primary tumor with metastasis.

Although identifying the origin of multiple tumors is challenging, it is important to distinguish whether tumors are single primary tumors with metastasis or multiprimary tumors. To increase the accuracy of the diagnosis, analyses of loss of heterozygosity, X-chromosome inactivation, mutation status, and single nucleotide polymorphisms have been attempted (Ikeda et al., 2012). We performed IHC because one of the features of SMMN-FGT has a similar molecular biological background. Mikami et al. showed the results of 6 SMMN-FGT cases with immunohistochemistry results, positive for HIK1083 and/or MUC6 and negative for MUC2, ER, and $p16^{INK4}$; the result of our case was similar to this previous report (Mikami et al., 2009).

Some patients with SMMN-FGT also have PJS, which can be associated with minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia (Mangili, 2004; Banno et al., 2013). PJS associated neoplasms may arise from genetic changes causing loss of function in

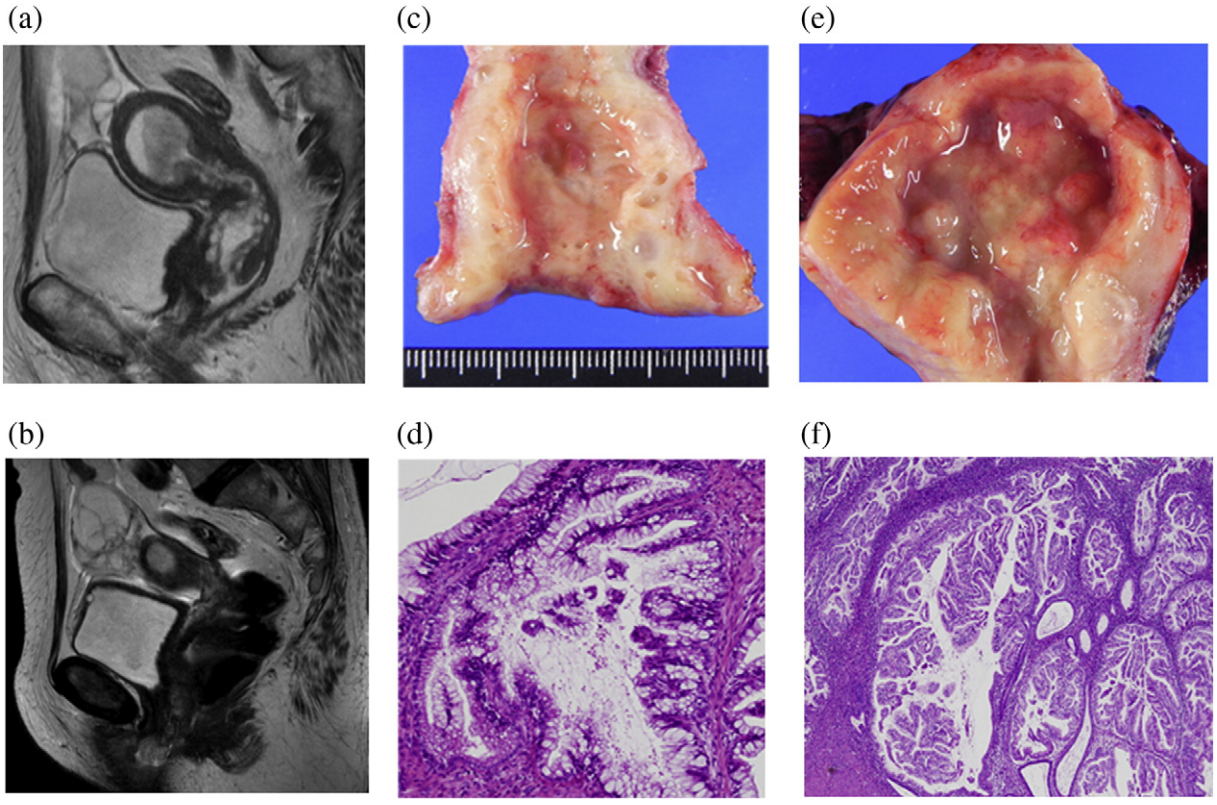

Fig. 2. Magnetic resonance imaging and resected uterus findings. (a) Multiple cystic lesions along the cervical canal. (b) Ovarian tumor and external urethral meatus neoplasm. (c) Enlarged cervical canal with multiple cysts on the wall. (d) Mucinous adenocarcinoma of the cervix. (e) Diffused tumor of the endometrium. (f) Noninvasive mucinous metaplasia of the endometrium.

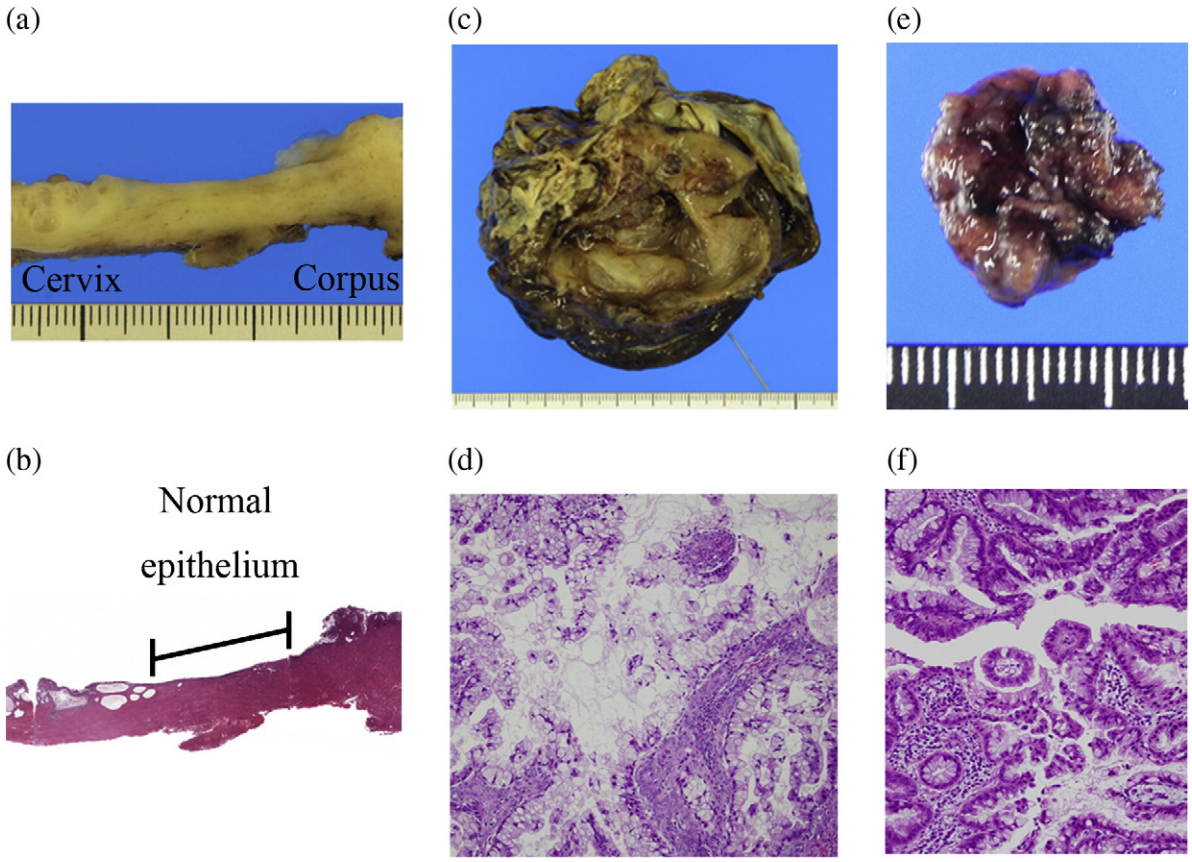

Fig. 3. Resected uterus, ovary, and urethral meatus neoplasm findings. (a, b) Lengthwise section of the uterus, (a) unstained, (b) stained with hematoxylin–eosin. No obvious continuity was noted between the cervical and endometrial neoplasms. (c) Multicystic ovarian tumor. (d) Ovarian tumor showed mucinous borderline tumor. (e) Solid mass at the urethral meatus. (f) Mucinous metaplasia with atypia was found in the urethral mass.

the tumor suppressor gene *STK11/LKB1* (Banno et al., 2013). In our case, the *STK11* mutation was not explored because colonoscopy findings showed no existing polyposis.

Mutations in *KRAS* have been reported in 89% of the endometrial mucinous adenocarcinoma, in contrast to only 14% in simple mucinous metaplasia (Yoo et al., 2012). *GNAS* encodes the alpha-subunit of the stimulatory guanine nucleotide-binding protein and leads to elevated intracellular cAMP levels (Landis et al., 1989). Recently, 42% of lobular endocervical glandular hyperplasia cases are shown to possess activating *GNAS* mutations (Matsubara et al., 2014). In our case, neither *KRAS* nor *GNAS* mutation was identified, indicating that the current case possessed no major mutations. Further studies are warranted to identify the genomic features in SMMN-FGT.

It is interesting to note that our case presented with a tumor at the external urethral meatus. To the best of our knowledge, this is the first report regarding SMMN-FGT with urethral neoplasm. Our case might indicate that synchronous mucinous metaplasia and neoplasia is arisen not only in female genital tract but also any locations such as urinary tract.

We realize that this is a case report with relatively low generalizability, and our opinions are partially based on our hypothesis. Therefore, analysis of a greater number of cases is required to clarify the etiology, adequate diagnostic method, treatment, and prognosis of SMMN-FGT.

Conclusion

We herein present a case of multiple mucinous metaplasia and neoplasia of the cervix, endometrium, fallopian tube, ovary, and mesenterium with external urethral meatus neoplasm. Immunohistochemistry showed almost the same pattern in each neoplasms, and PCR-direct sequencing showed no existence of both *KRAS* and *GNAS* mutations. This report suggests a diagnostic usefulness of immunohistochemistry for SMMN-FGT, and a possibility of this disease "beyond" female genital tract. Careful assessment including the urinary tract should be performed in multiple female genital tract neoplasms.

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Table 1
Immunohistochemical analysis for each neoplasm.

	Invasion	HIK1083	MUC2	MUC5AC	MUC6	HGM	CDX2	p16	ER
Cervix	Invasive	+	−	+	+	+	−	−	−
Endometrium	Invasive	+	−	+	+	+	−	−	+/−
Ovary	Invasive	+	−	+	+	+	−	−	−
Urethra	Invasive	+	+/−	+	+	+	−	−	−
Gastric	Non-invasive	−	+/−	−	−	−	+	NA	−

N/A: not available.

Conflict of interest statement

No authors declare competing interests.

Patient consent

The patient gave written consent for the case report to be published.

Financial disclaimer

None.

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