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A case of low-grade intestinal-type mucinous neoplasm of the fallopian tube with KRAS exon 2 mutation

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ABSTRACT

Several types of mucinous lesions of the fallopian tube have been reported, including metaplastic and neoplastic lesions, most of which exhibit gastric phenotypes. Here, we report a unique case of a mucinous tumor arising in the right fallopian tube of a 36-year-old female who presented with refractory abdominal pain for approximately one year. Abdominal CT and MRI found a cystic lesion leading to the diagnosis of hematosalpinx, thus right salpingo-oophorectomy and appendectomy were performed. Macroscopic findings included cystic dilatation of the distal portion of the right fallopian tube, filled with gelatinous mucin. Histologically, mucinous columnar cells proliferated in papillary configurations in the cystic region without invasion, resembling low-grade appendiceal mucinous neoplasms. Immunohistochemical analysis revealed that the neoplastic cells expressed CDX-2 and SATB2, but not WT-1, PAX8, ER, PgR, or claudin 18. Sanger sequencing of the mucinous lesion identified a KRAS exon 2 mutation (p.G12A), confirming similar pathologic and genetic characteristics to ovarian mucinous borderline tumors. This rare low grade intestinal-type mucinous tumor indicates the fallopian tube epithelium can give rise to tumors resembling low-grade appendiceal mucinous neoplasms and cause pseudomyxoma peritonei without appendiceal lesions.

1. Introduction

One of the breakthrough advances in gynecologic oncology is the identification of the fallopian tube as a source of high-grade serous carcinoma. Serous carcinoma originating from the fallopian tube has turned out to be much more frequent than previously thought, and the SEE-FIM (Sectioning and Extensively Examining the FIMbriated end of the fallopian tube) protocol is widely accepted as the standard for examination of pelvic cancers. The fallopian tube also develops mucinous lesions, albeit much less frequently, and both neoplastic and metaplastic lesions have been reported (Seidman, 1994; Mikami et al., 2009; Wong et al., 2011; Wheal et al., 2017). Here, we report a unique case of a mucinous neoplasm originating in the fallopian tube. The tumor closely resembled low-grade appendiceal mucinous neoplasm morphologically and harbored a KRAS mutation; however, extensive examination did not identify any neoplastic lesion in the appendix. This case not only expands the spectrum of tubal neoplasms, but also indicates a possible tubal origin of pseudomyxoma peritonei, in the absence of appendiceal neoplasm.

2. Case report

A 36-year-old woman was referred to our hospital for persistent refractory abdominal pain that had lasted for approximately one year. She had no significant medical history and was diagnosed with right hematosalpinx based on pelvic CT and MRI imaging (Fig. 1). No tumor was identified in bilateral ovaries. Except for her grandmother who died from pancreatic cancer, she had no significant family history of the disease, and had not undertaken any genetic testing. In our hospital, colonoscopy was performed to reveal no tumor, and the laboratory test results showed no elevations of tumor markers as follows; CA125, 2.2 ng/ml; CA19-9, 8.2 U/ml; CA125 17.1U/ml. She underwent right salpingo-oophorectomy. During the operation, a large cystic lesion was identified in the pelvic cavity. The lesion appeared to be a cystic dilatation of the distal portion of the right fallopian tube. The apical portion of the normal-sized appendix was loosely attached to the cystic lesion.

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Considering the possible association between the cystic lesion and the appendix, an appendectomy was also performed. The cyst wall did not rupture, and mucus retention was not observed in the peritoneal cavity. Peritoneal washing was not performed.

3. Pathologic findings

Macroscopic examination confirmed that the cystic lesion was an extensive dilatation of the distal portion of the right fallopian tube, which contained abundant mucin, while the proximal portion of the tube was of normal size (Fig. 2A, B). There was no communication between the cystic lesion and appendix. Cross sections of the appendix and the fallopian tube were thoroughly and extensively dissected for microscopic examination. Histologically, the inner surface of the cyst was covered with mucinous columnar cells showing papillary or low papillary proliferation (Fig. 2C). Mucinous cells exhibited mild-to-moderate atypia with stratified, enlarged nuclei. Denudation of the mucinous epithelia and intramural mucin leakage were focally noted, but no infiltrative growth of mucinous epithelial cells was identified (Fig. 2D). Interestingly, transition from neoplastic columnar cells to tubal epithelium was observed (Fig. 2E, F). No proliferative epithelium or mucus retention was observed in the appendix, which showed fibrous obliteration at the apical portion and presented neither diverticulum-like nor outpouching lesion (Fig. 2G, H). These histological findings strongly supported that the cystic lesion was mucinous borderline tumor derived from the fallopian tube, not the appendix. Despite detailed examination of the fallopian tube, fimbria was not identified.

Immunohistochemically, the mucinous cells of the cystic lesion were positive for CK 20, CDX-2, and SATB2 but negative for PAX8, ER, PgR, and claudin 18 (Fig. 3A-G). The Ki-67 labeling index was 10% at the hotspot (Fig. 3H). The adjacent tubal epithelium and subepithelial stromal cells were positive for ER and PgR expression (Fig. 3E, F). These findings led us to diagnose low-grade intestinal-type mucinous neoplasm originating from the fallopian tube. No neoplastic or metaplastic lesions were observed in the right ovary.

Considering that KRAS mutations are frequent in colorectal carcinomas, including those with mucinous differentiation (Rosty et al., 2013; Li et al., 2020) and ovarian mucinous tumors (Ichikawa et al., 1994; Enomoto et al., 1991; Garrett et al., 2001), we conducted mutational analyses. We analyzed the DNA extracted from mucinous glands by microdissection (Fig. 4A, B). Sanger sequencing revealed a KRAS p.G12A mutation in the neoplastic epithelia (Fig. 4C). KRAS exon 2 mutations were not found in the adjacent non-tumoral tubal epithelia (Fig. 4D). Appendiceal epithelia were also tested, but KRAS exon 2 mutations were not found (data not shown). While pathological and genetic findings strongly supported a diagnosis of mucinous borderline tumor for our case, KRAS mutations have been reported as an early event in the development of ovarian mucinous carcinoma, indicating this tumor's potential for malignant transformation (Morice et al., 2019). Thus, follow-up was scheduled according to NCCN guidelines for ovarian cancer (Salani et al., 2017): visits every four months for two years, then every six months for three years, followed by annual visits after five years. At the most recent follow-up visit, two years and seven months post-surgery, the patient remained disease-free with no evidence of recurrence.

4. Discussion

We present a unique case of intestinal-type mucinous neoplasm arising in the fallopian tube, with a morphological appearance resembling that of low-grade appendiceal mucinous neoplasms. Several groups have reported mucinous lesions in fallopian tubes. Seidman reported seven cases of mucinous lesions, including metaplasia, benign cystadenoma, borderline tumor, and carcinoma in situ with metaplasia (Wong et al., 2011). Two cases in the series were associated with Peutz-Jeghers syndrome. Synchronous and multifocal mucinous metaplasia and neoplasia of the female genital tract frequently develop mucinous metaplasia in the fallopian tube and occasionally show features of borderline malignancy (Mikami et al., 2009). Metaplastic papillary tumors are unique tumors frequently associated with pregnancy and are characterized by papillary growth of oncolytic and mucinous metaplastic epithelia (Saffos et al., 1980). In addition, two cases of mucinous adenocarcinoma have recently been reported (Wheal et al., 2017). Notably, these previous reports indicate that both metaplastic and neoplastic lesions frequently exhibit a gastric phenotype (Mikami et al., 2009; Wheal et al., 2017). The present case differs from previously

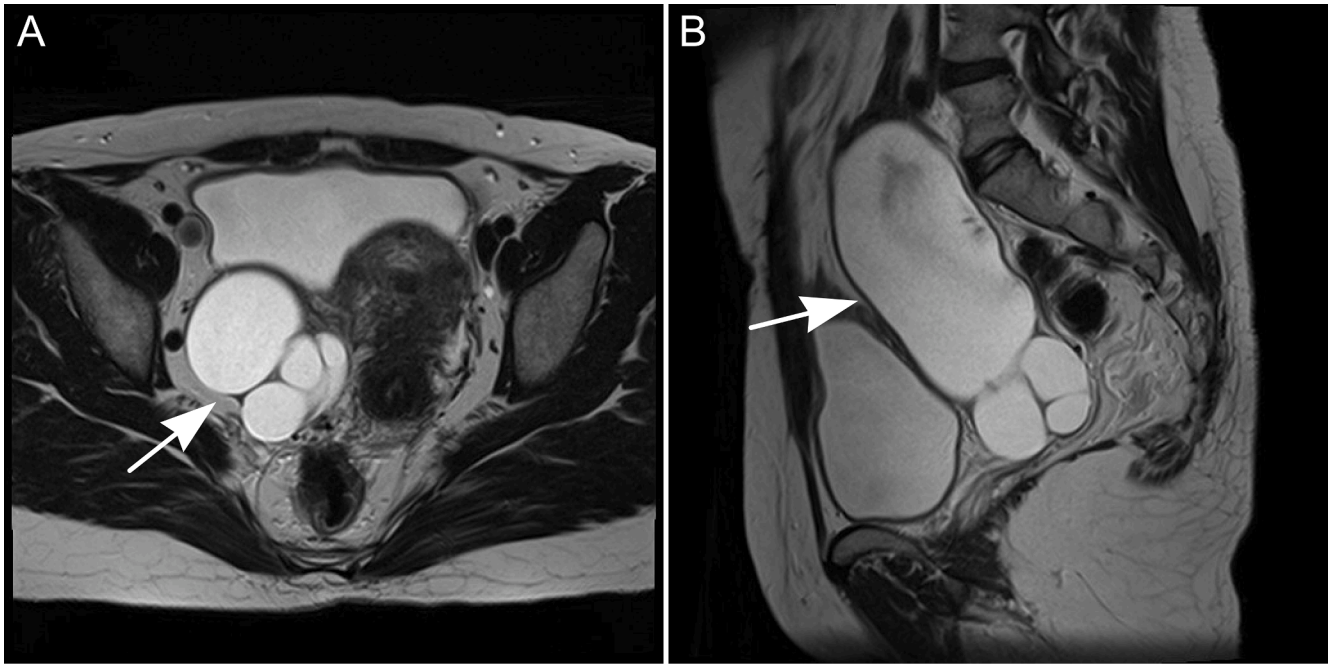

Fig. 1. Pelvic T2-weighted MRI demonstrated a dilated tubular structure on the right side of the uterus, measuring approximately 14.0 × 6.0 × 5.5 cm (arrows). The sagittal image exhibited focal T2 shading in the dilated lumen (B), indicative of right hematosalpinx.

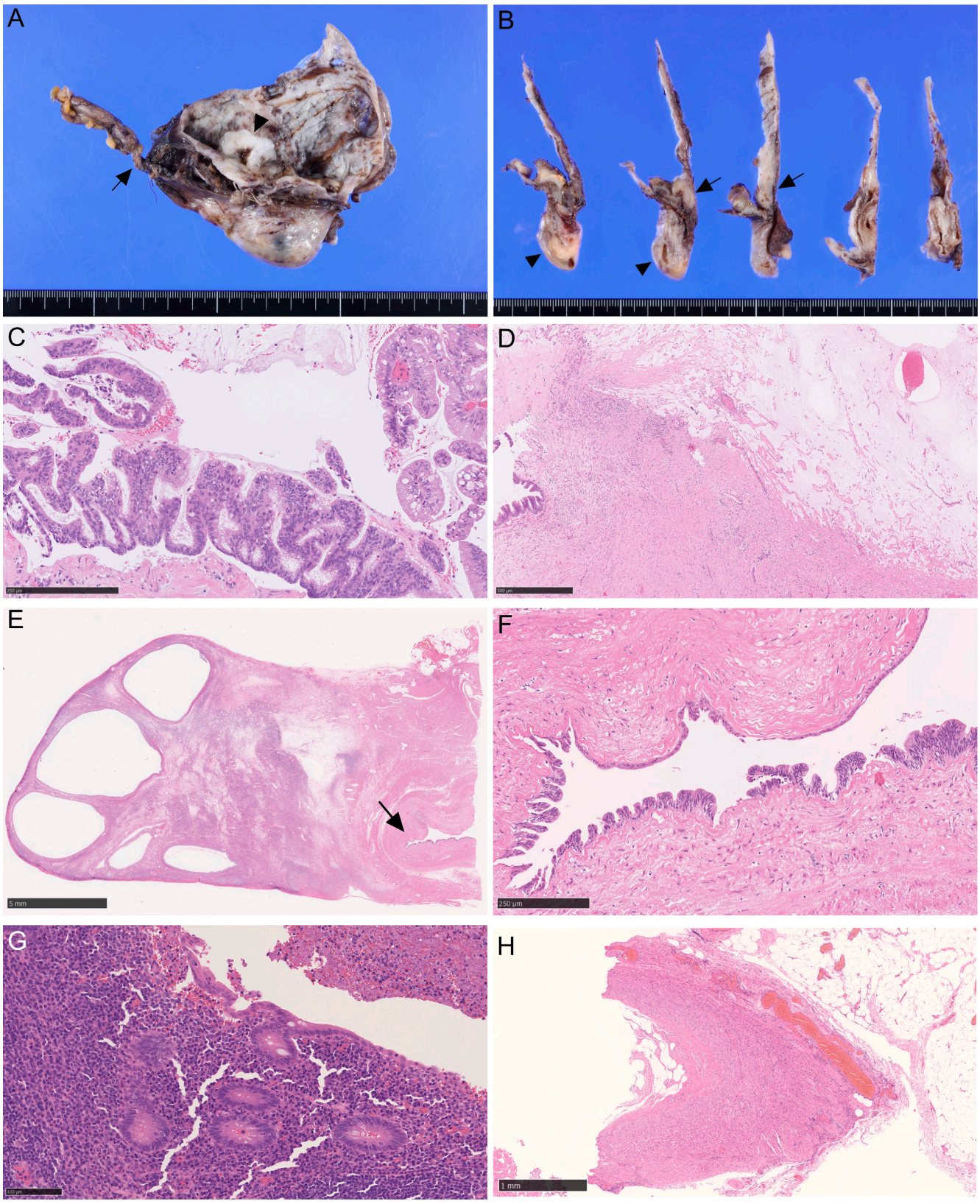

Fig. 2. Pathologic findings for the resected right uterine adnexa and appendix. (A) Macroscopically, the distal portion of the right fallopian tube was extensively dilated, containing abundant mucin (arrowhead). The appendix was attached to the cystic part via a fibrous band (arrow). (B) Cut surfaces of the cystic part. The proximal portion of the tube was not dilated (arrows) and the right ovary contained no tumor (arrowheads). (C) Microscopically, the cyst wall was lined with papillary proliferation of mucinous columnar cells. Bar = 250 μm. (D) The mucin pool without epithelial lining was formed in the cyst wall. Bar = 500 μm. (E) Low-power view demonstrating the right ovary and fallopian tube (arrow). Bar = 5 mm. (F) High-power image of the arrow in the Fig. 1E showing transition between neoplastic papillary columnar cell and normal flat tubal epithelium. Bar = 100 μm. (G) The appendix mucosa showing no atypical epithelium or mucus retention. Bar = 100 μm.. (H) The distal end of the appendix presenting fibrous obliteration and no appendiceal mucosa was identified. Bar = 1 mm.

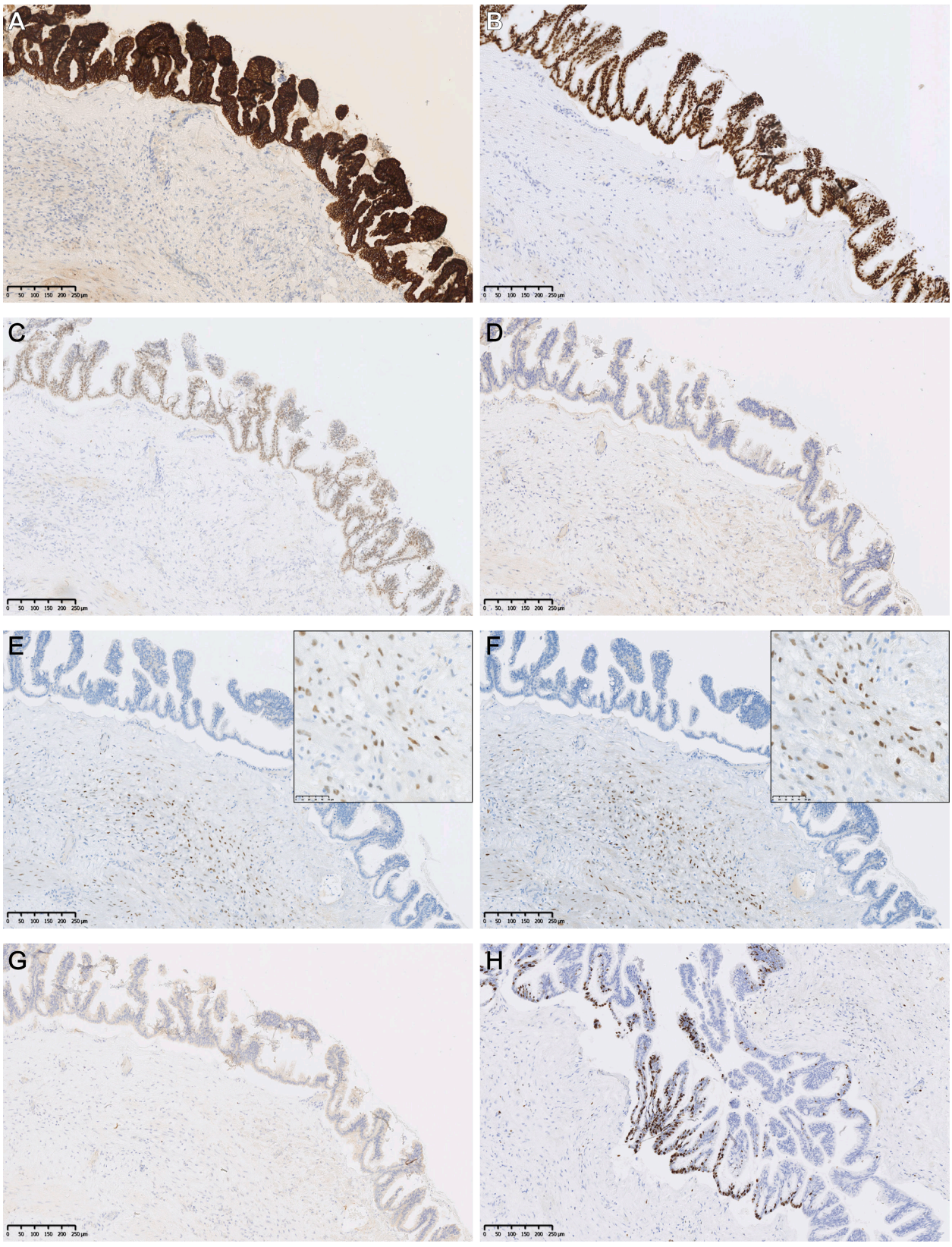

Fig. 3. Immunohistologic profile of the mucinous tumor using CK 20 (A), CDX-2 (B), SATB2 (C), PAX8 (D), ER (E), PgR (F), Claudin-18 (G), and Ki-67 (H) (Bar = 250 μm). Insets: high power view of stromal cells beneath the epithelia (Bar = 50 μm).

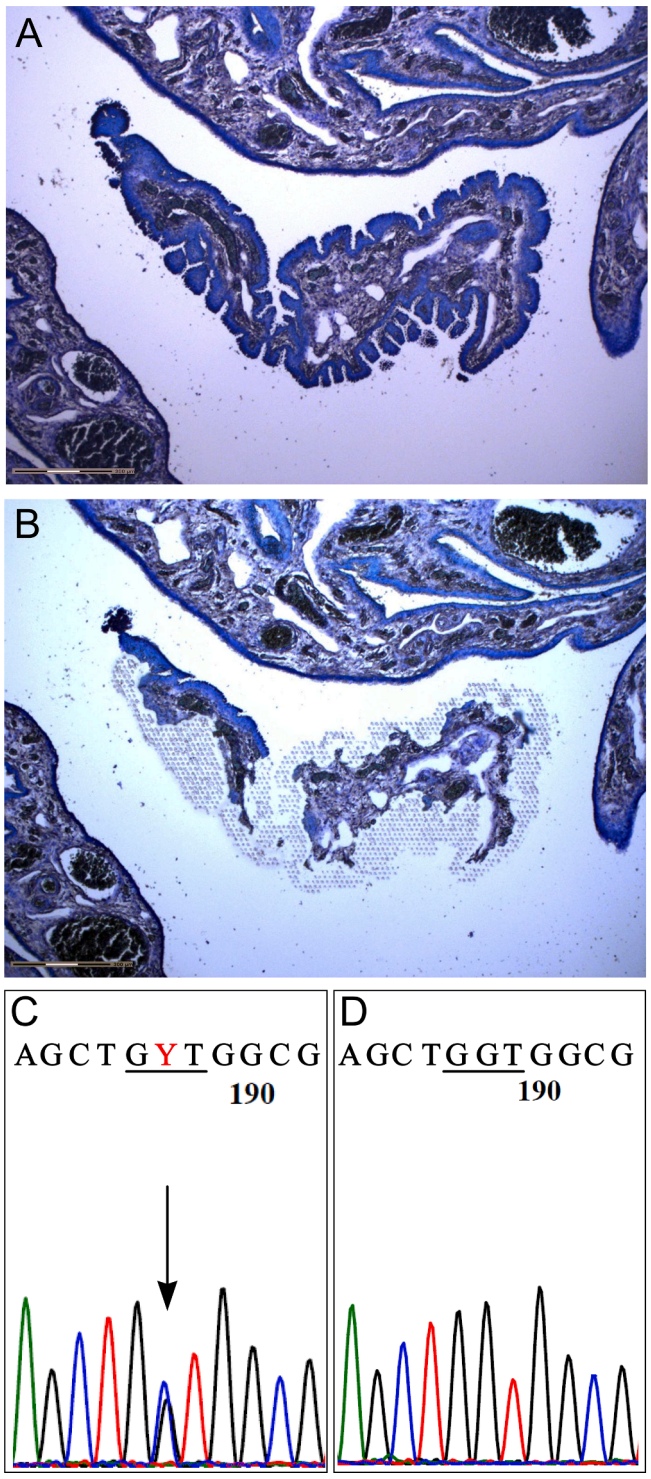

Fig. 4. (A, B) Representative photomicrographs of the microdissection. Tissue sections of mucinous tumor before (A) and after (B) laser capture microdissection. (C, D) Sanger sequencing validation of exon 2 of the KRAS gene. p. G12A missense mutation is detected in mucinous epithelia (C), while no mutation is found in the adjacent non-atypical fallopian tube epithelia (D). Underbar represents codon 12 and the missense mutation is indicated by an arrow.

reported mucinous lesions based on morphological and phenotypic aspects.

Considering the morphological appearance of the present tumor, its appendiceal origin should be carefully ruled out. In this case, extensive examination revealed no atypical appendiceal epithelia related to the cystic tumor and no KRAS mutation was identified by Sanger sequencing. Moreover, the presence of ER- and PgR-positive stromal cells strongly indicated that the cystic wall consisted of fallopian tube.

Although mucin retention was not observed in the peritoneal cavity, intramural mucin leakage in this case indicates that mucinous tumors of the fallopian tube could be a potential cause of pseudomyxoma peritonei. The majority of pseudomyxoma peritonei cases are derived from low-grade appendiceal mucinous neoplasms, while various other primary sites such as the gastrointestinal tract, urachus, pancreas, and lung have been reported (Lemahieu et al., 2013; de Bree et al., 2000; Chejfec et al., 1986; Kurita et al., 1994). There has been no pseudomyxoma peritonei of fallopian tube origin in the English literature.

In summary, we present a case of mucinous neoplasm of the fallopian tube harboring a KRAS mutation consistent with intestinal-type mucinous borderline tumor. Morphologically, this neoplasm resembled low-grade appendiceal mucinous neoplasms. This case expands the spectrum of mucinous lesions of the fallopian tube and indicates a possible origin of pseudomyxoma peritonei in the absence of low-grade appendiceal mucinous neoplasms. KRAS G12 mutated-carcinomas could be therapeutic targets of KRAS inhibitors such as adagrasib, which has been recently reported to show clinical efficiency for previously treated non-small cell lung carcinoma with KRAS G12C mutation (Jänne et al., 2022).

Conflict of interest and source of funding

The authors have declared that no conflict of interest exists. This work was supported by JSPS KAKENHI Grant Number 21 K06930.

Author contribution

KN, AI, and JS performed the histological examination of the resected specimen and made the histological dianosis. KN performed and collected the data of DNA sequencing. KN wrote the manuscript with support from AH and JS. MM and YK analyzed and interpreted the patienta data. They also performed the operation thus to contribute the diagnosis. All authors read and approved the final manuscript.

Informed consent: Informed consent was obtained from the patient to be included in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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