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Clinicopathological Characteristics of Metaplastic Papillary Tumor of the Fallopian Tube

MI JANG[1], JI-YOUN SUNG[2], JI-YE KIM[1,3] and HYUN-SOO KIM[1]

[1]*Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea;*
[2]*Department of Pathology, Kyung Hee University College of Medicine, Seoul, Republic of Korea;*
[3]*Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*

Abstract. *Metaplastic papillary tumor (MPT) of the fallopian tube is a very uncommon lesion, displaying papillary growth of bland-appearing cells with abundant, eosinophilic cytoplasm and mucinous metaplasia. It is difficult for pathologists to determine whether to categorize this lesion as a metaplastic proliferative lesion or a true neoplasm. We recently experienced a case of tubal MPT and initiated a comprehensive review of previously published cases with thorough analysis of clinicopathological characteristics. MPT is typically related to pregnancy, but we describe the first case of pregnancy-unrelated, incidentally detected tubal MPT in a 51-year-old woman who underwent surgery for endometrial cancer. The MPT consisted of small papillary formations with epithelium consisting of nonciliated, columnar cells with abundant eosinophilic cytoplasm arranged as either a single layer or pseudostratified layer. The stroma had a myxoid appearance. Intraluminal and extracellular mucin and floating papillary tufts were observed. Nuclei of the epithelial lining cells were centrally located, rounded or oval, and displayed intranuclear pseudoinclusions or grooves. The MPT cells were positive for paired box 8, epithelial membrane antigen, and cytokeratin. Interestingly, Wilms tumor 1 (WT1) protein was localized within the cytoplasm of MPT cells. Furthermore, the MPT cells did not express phosphatase and tensin homolog deleted on chromosome 10 (PTEN). In summary, MPT of the fallopian tube is a very unusual, distinctive entity displaying unique histopathological features and immunophenotype. Our observation of cytoplasmic WT1 expression and loss of PTEN expression in tubal MPT suggests its neoplastic nature and raises the possibility of WT1 or PTEN involvement in the development of MPT.*

Correspondence to: Hyun-Soo Kim, Department of Pathology, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Tel: +82 222281794, +82 23620860, e-mail: hyunsookim@yuhs.ac

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Fallopian tube epithelium can undergo metaplastic, hyperplastic, and neoplastic changes. Reported metaplastic changes include squamous metaplasia, oncocytic metaplasia, transitional cell metaplasia, and mucinous metaplasia (1-4). These changes are found both with and without associated tubal inflammation or history of exogenous hormone use. Hyperplastic or proliferative changes of the tubal epithelium have also been reported in association with endometriosis or tubal inflammation, especially tuberculous salpingitis (5, 6).

Metaplastic papillary tumor (MPT) is an extremely rare lesion of the fallopian tube. Only 11 cases of tubal MPT have been documented in the previous literature to date (7-14). Tubal MPT has been reported to be closely related to pregnancy because it is found upon examination of fallopian tube segments removed for sterilization in the immediate postpartum period. This lesion is morphologically characterized by a papillary growth pattern, oncocytic and mucinous metaplasia, and lack of cytological atypia or mitosis. Debate exists about whether this lesion represents a true neoplasm or a metaplastic proliferative lesion. Due to its rarity and small size, tubal MPT can be a diagnostic challenge for pathologists.

We recently experienced a case of tubal MPT in a nonpregnant, postmenopausal woman who underwent surgery for endometrial cancer. Upon review of the previous literature and standard textbooks, very little detailed clinically useful information was found concerning this lesion. We thoroughly reviewed previously published cases to clarify their clinicopathological characteristics, immunohistochemical staining results, and coexisting medical problems. Comprehensive analyses of MPT cases may expand our knowledge regarding MPT of the fallopian tube.

Materials and Methods

Case presentation. A 51-year-old woman presented with persistent vaginal bleeding. Her past medical history was unremarkable. Transvaginal ultrasonography revealed an abnormally thickened endometrium. The endometrial curettage specimen showed International Federation of Gynecology and Obstetrics (FIGO) grade 2 endometrioid carcinoma. An abdominopelvic magnetic resonance imaging scan revealed no evidence of abdominopelvic peritoneal seeding. No evidence of pelvic or para-aortic lymph node metastases was noted. Chest computed tomographic scan revealed no evidence of metastases in the lung, liver, or mediastinum. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and appendectomy. The postoperative course was uneventful, and the patient was discharged after a full recovery. To date, she is healthy and without any complaints. No evidence of tumor recurrence has been detected.

Histopathological examination. The resection specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin blocks. From each formalin-fixed, paraffin-embedded tissue block, 4 μm sections were cut and stained with hematoxylin and eosin. All available hematoxylin and eosin-stained slides were examined by routine light microscopy, and the most representative formalin-fixed, paraffin-embedded block was chosen to perform immunohistochemical staining and mutational analyses.

Immunohistochemistry. Four-micrometer-thick sections of 10% neutral formalin-fixed, paraffin-embedded blocks were deparaffinized and rehydrated with a xylene and alcohol solution. Immunohistochemical staining was performed using the Ventana Benchmark XT automated staining system (Ventana Medical Systems, Inc., Tucson, AZ, USA) or Dako Omnis (Dako, Agilent Technologies, Inc., Carpinteria, CA, USA) according to the manufacturer's instructions. Antigen retrieval was performed using Cell Conditioning Solution (CC1; Ventana Medical Systems, Inc.) or EnVision FLEX Target Retrieval Solution, High pH (Dako, Agilent Technologies, Inc.). Tissue sections were subsequently incubated with primary antibodies against epithelial membrane antigen (EMA; 1:200; clone E29; Dako), pan-cytokeratin (CK;1:600; clone AE1/AE3; Dako), paired box 8 (PAX8; 1:50; polyclonal; Cell Marque), Wilms tumor 1 (WT1; 1:200; clone 6F-H2; Cell Marque, Rocklin, CA, USA), p16 (prediluted; clone E6H4; Ventana Medical Systems), p53 (1:300; clone DO-7; Novocastra, Leica Biosystems, Newcastle Ltd., Newcastle Upon Tyne, UK), estrogen receptor (ER; 1:150; clone 6F11; Novocastra), progesterone receptor (PR; 1:100; clone 16; Novocastra), human epidermal growth factor receptor 2 (HER2; prediluted; clone 4B5; Ventana), phosphatase and tensin homolog deleted on chromosome 10 (PTEN; 1:100; clone D4.3; Cell Signaling Technology, Danvers, MA, USA), CK7 (1:100; clone OV-TL 12/30; Dako), CK20 (1:100; clone Ks20.8; Dako), caudal-related homeobox 2 (CDX2; 1:400; clone EPR2764Y; Cell Marque), Ki-67 (1:150; clone MIB-1; Dako), mutL homolog 1 (MLH1; prediluted; clone M1; Ventana), mutS homolog 2 (MSH2; prediluted; clone G219-1129; Cell Marque), MSH6 (1:100; clone 44, Cell Marque), and PMS1 homolog 2 (PMS2; 1:40; clone MRQ28; Cell Marque). After the chromogenic visualization step using the ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc.) or EnVision FLEX /HRP (Dako, Agilent Technologies, Inc.), slides were counterstained with hematoxylin and coverslipped. Appropriate positive and negative controls were concurrently stained to validate the staining procedure.

DNA extraction. Genomic DNA was extracted from 4 μm sections of 10% neutral formalin-fixed, paraffin-embedded tissue blocks using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). The concentration and purity of extracted DNA was determined by a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). The extracted DNA was stored at –20˚C until use.

Peptide nucleic acid (PNA)-mediated clamping polymerase chain reaction (PCR) for detection of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations. The assays for detection of seven different *KRAS* and *BRAF* variants were performed using the PNAClampTM KRAS and PNAClampTM BRAF Mutation Detection kits (Panagene, Inc., Daejeon, Republic of Korea), respectively (22). All reactions were performed in 20-μl volumes using 10–25 ng template DNA, primer, and PNA probe set, and SYBR Green PCR master mix. All required reagents were included with the kits. Real-time PCR reaction of PNA-mediated clamping PCR was performed using a CFX96™ Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., Hercules, CA, USA). PCR cycling conditions were a 5 min hold at 94˚C followed by 40 cycles at 94˚C for 30 s, 70˚C for 20 s, 63˚C for 30 s, and 72˚C for 30 s. Detection of each of seven mutations in the *KRAS* gene and one mutation in the *BRAF* gene was possible using one-step PNA-mediated real-time PCR clamping. In this assay, PNA probes and DNA primers were used together in the clamping reaction. Positive signals were detected by intercalation of SYBR Green fluorescent dye. The PNA probe sequence, which was complementary to wild-type DNA, suppressed amplification of wild-type targets, thereby enhancing preferential amplification of mutant sequences by competitively inhibiting DNA primer binding to wild-type DNA. PCR efficiency was determined by measuring the threshold cycle (Ct) value. Ct values for control and mutation assays were obtained by observing the SYBR Green amplification plots. Delta Ct (Δ Ct) values were calculated as follows, ensuring that the sample and standard Ct values were from the tested sample and clamping control sample: [Standard Ct] − [sample Ct]=Δ Ct. The cut-off Δ Ct was defined as 2 for *KRAS* and *BRAF* mutations.

Literature search. We thoroughly searched the Medline database using the PubMed retrieval service. Searches were performed in March 2017, using the key words "fallopian tube", "tube", "salpinx", and "metaplastic papillary tumor."

Results

Pathological findings MPT of the fallopian tube. The hysterectomy specimen showed a 3.5 × 3.0 cm FIGO grade 2 endometrioid carcinoma involving less than half of the myometrium (FIGO stage IA). No evidence of cervical stromal extension, serosal or parametrial extension, or vaginal extension was observed. No lymphovascular space invasion was noted. Bilateral pelvic lymph nodes were free of metastatic carcinoma. The bilateral ovaries, left fallopian tube, and appendix were unremarkable. Grossly, the lumen of the right fallopian tube contained an exophytic, papillary lesion, 0.5 cm

in its greatest dimension (Figure 1A). The lesion was present in two of eight cross sections and involved approximately half of the cross-sectional area. Histopathologically, the lesion consisted of small papillary formations with a connectival axis (Figure 1B). In contrast to normal tubal plicae, the epithelial lining of the lesion appeared to have abundant, eosinophilic cytoplasm at low power magnification. The stroma had a pale blue appearance due to myxoid change (Figure 1C). The papillary cores were relatively thin and sometimes edematous, with loose fibrovascular connective tissues that contained occasional small blood vessels, sparse lymphocytes, and rare neutrophils (Figure 1D). Epithelial cells were confined to the surfaces of the papillae. Epithelial cells were columnar and nonciliated and were arranged as either a single layer of uniform cells or a pseudostratified layer of cells with nuclei at various levels (Figure 1E). Intraluminal mucin, extracellular mucin, and floating papillary tufts were observed. These tufts also contained fibrovascular cores showing small blood vessels and lymphocytic infiltration (Figure 1F). Epithelial elements tended to bud from the epithelial lining, detaching from papillae. These atypical epithelial elements showed abundant eosinophilic cytoplasm and slight nuclear pleomorphism. In some areas, papillary excrescences protruding into the lumen resembled those of ovarian serous borderline tumor. The hyalinized or myxoid stroma was lined with a single layer of columnar epithelium (Figure 1G). At high-power magnification, most epithelial cells did not show significant nuclear pleomorphism. The nuclei of these cells were centrally located, rounded, or oval. In a few areas, however, the nuclei displayed a variable appearance, with either dense or vesicular chromatin, a small or prominent nucleolus, intranuclear pseudoinclusions (Figure 1H), intranuclear grooves or folds, and membrane irregularities. Intracytoplasmic basophilic granules (Figure 1I), psammomatous microcalcifications (Figure 1J), and apical cytoplasmic blebs or snouts (Figure 1K) were also occasionally observed.

Immunohistochemical findings of MPT of the fallopian tube. Immunohistochemical staining results are summarized in Table I. MPT cells and normal tubal epithelium were diffusely and strongly positive for EMA, pan-cytokeratin (CK), CK7, and PAX8. They were also uniformly immunoreactive for ER (Figure 2A). In contrast, PR immunoreactivity of MPT cells was reduced compared to that of normal tubal epithelium (Figure 2B). MPT showed patchy p16 expression (Figure 2C). In particular, p16 protein was localized within both the nuclei and cytoplasm of MPT cells (Figure 2D). WT1 immunoreactivity of MPT cells was distinct from that of normal tubal epithelium (Figure 2E). Approximately half of MPT cells had strong to moderate cytoplasmic WT1 expression (Figure 2F). Some MPT cells displayed weak WT1 expression with a perinuclear dot-like pattern (Figure 2G). In contrast, normal tubal epithelium exhibited strong to moderate nuclear WT1 immunoreactivity (Figure 2H). There was also a significant difference in PTEN expression between MPT and normal tubal epithelium (Figure 2I). MPT cells did not react for PTEN (*i.e.* exhibiting loss of PTEN expression; Figure 2J), whereas normal tubal epithelium showed cytoplasmic PTEN expression (Figure 2K). Ki-67 labeling index was less than 1% in MPT (Figure 2L). MPT revealed a wild-type p53 immunostaining pattern (patchy distribution and weak intensity; Figure 2M). MPT cells were weakly positive for CK20 and negative for CDX2 and human epidermal growth factor receptor 2 (HER2; Figure 2N). There was no loss of expression of mismatch repair proteins MLH1, MSH2, MSH6 and PMS2.

Table I. *Immunostaining results of our case of tubal metaplastic papillary tumor.*

Antibody	Location of staining	Result
EMA	Membrane	Strongly positive
Pan-CK	Membrane	Strongly positive
PAX8	Nucleus	Strongly positive
WT1	Cytoplasm	Strongly to moderately positive
p16	Nucleus and cytoplasm	Moderately to weakly positive
p53	Nucleus	Moderately to weakly positive
ER	Nucleus	Strongly positive
PR	Nucleus	Weakly positive
HER2	Not applicable	Negative
PTEN	Not applicable	Negative (loss of expression)
CK7	Membrane	Strongly positive
CK20	Membrane	Weakly positive
CDX2	Not applicable	Negative
Ki-67	Nucleus	Moderately to weakly positive (less than 1%)
MLH1	Nucleus	Moderately positive (no loss of expression)
MSH2	Nucleus	Moderately positive (no loss of expression)
MSH6	Nucleus	Moderately positive (no loss of expression)
PMS2	Nucleus	Moderately positive (no loss of expression)

CDX2: Caudal-related homeobox 2, CK: cytokeratin, EMA: epithelial membrane antigen, ER: estrogen receptor, HER2: human epidermal growth factor receptor 2, MLH1: mutL homolog 1, MSH2: mutS homolog 2, MSH6: mutS homolog 6, PAX8: paired box 8, PMS2: PMS1 homolog 2, PR: progesterone receptor, PTEN: phosphatase and tensin homolog, WT1: Wilms tumor 1.

Mutational analysis of MPT of the fallopian tube. PNA-mediated PCR clamping found no mutations in *KRAS* or *BRAF* genes in this case of left tubal MPT.

Discussion

MPT of the fallopian tube is typically recognized in postpartum state at the time of tubal ligation for sterilization. It is morphologically characterized by papillary growth of

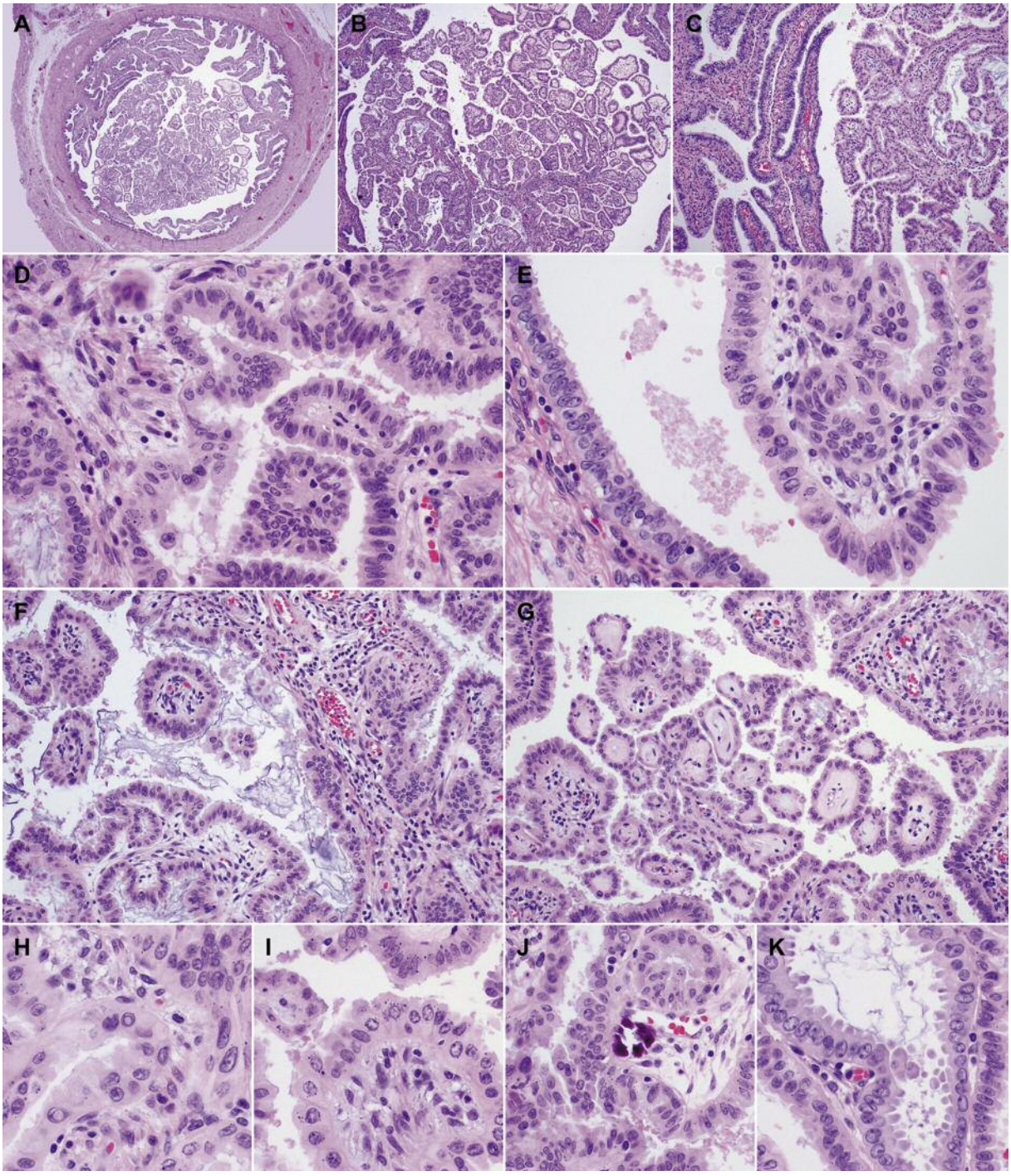

Figure 1. *Histopathological findings of metaplastic papillary tumor of the fallopian tube. A: Low-power view of hematoxylin and eosin staining reveals exophytic mass within the tubal lumen, involving only part of the mucosal circumference. B: The mass had a papillary configuration in part due to its origin from the tubal plicae and occupied approximately half of the lumen. C: In contrast to normal tubal plicae (left half), papillary cores (right half) were pale blue with an edematous, myxoid appearance. D: They consisted of loose fibrovascular connective tissue containing small numbers of inflammatory cells, mostly lymphocytes. E: The epithelial lining comprised of one to two layers of plump, nonciliated columnar cells with abundant, eosinophilic cytoplasm. F: Intraluminal extracellular mucin can be seen admixed with variably sized, floating, round papillary tufts containing fibrovascular cores. G: Some areas showed aggregation of small papillae with hyalinized or myxoid stroma lined with a single layer of columnar epithelium, resembling those of ovarian serous borderline tumor. H: In a few areas, nuclei were found to be arranged haphazardly within the cytoplasm and often contained a small nucleolus. I-K: Intranuclear cytoplasmic pseudoinclusions were frequently observed. Also seen were intracytoplasmic basophilic granules (I), psammomatous microcalcifications (J) and apical cytoplasmic snouts or blebs (K). Original magnification: A, ×12.5; B-C, ×40; D-E, ×200; F-G, ×100; H-K, ×200.*

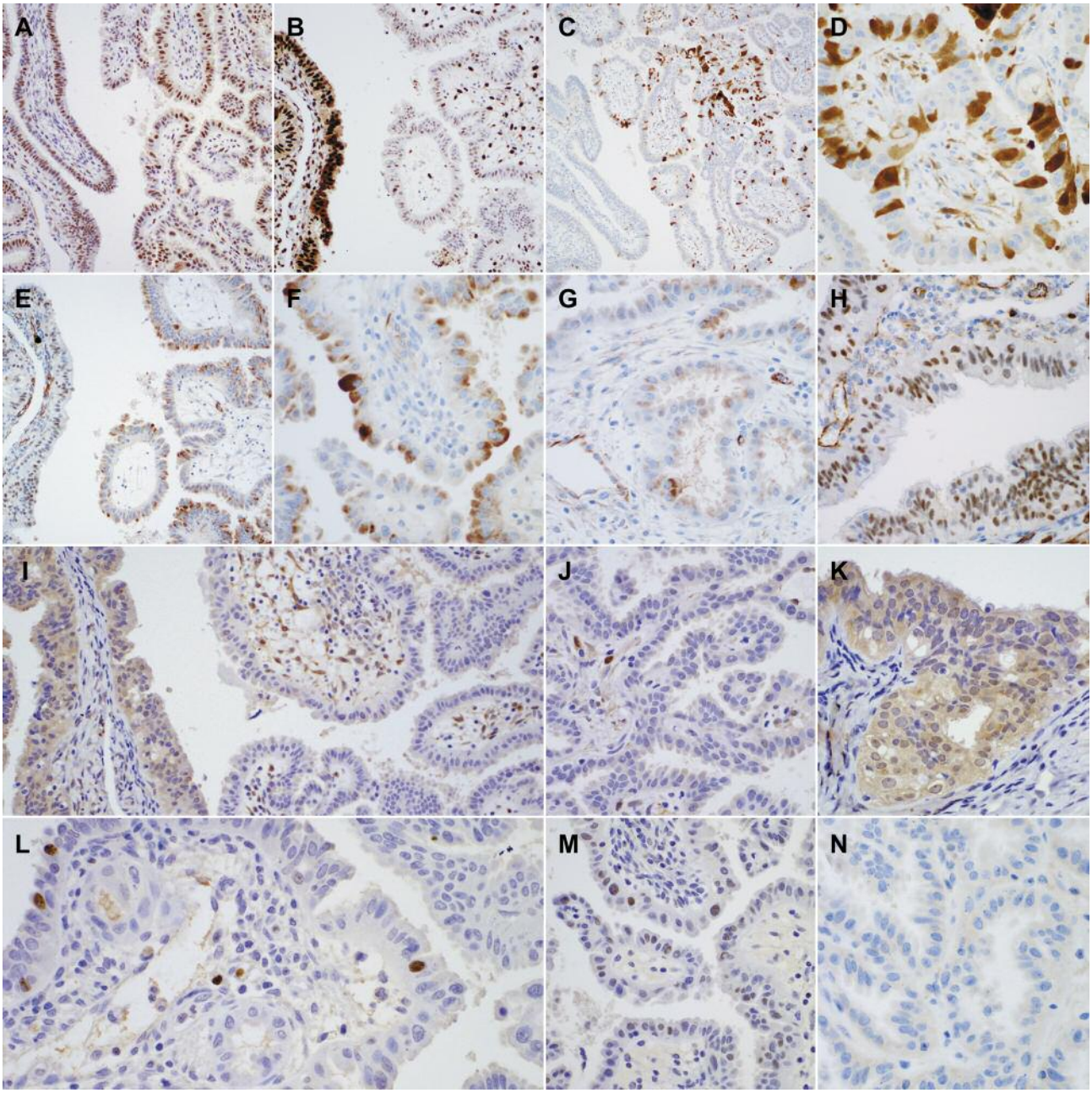

Figure 2. *Immunohistochemical findings of metaplastic papillary tumor (MPT) of the fallopian tube. A: Both MPT (right two-thirds) and normal tubal epithelium (left one-third) were found to be positive for estrogen receptor. B: Progesterone receptor immunoreactivity was lower in MPT cells (right half) compared to that of estrogen receptor. C: MPT cells (right two-thirds) displayed patchy p16 expression. D: High-power magnification demonstrated that p16 was localized in both the nuclei and cytoplasm of MPT cells. E: There was a significant difference in the location of Wilms tumor 1 (WT1) expression between MPT and normal tubal epithelium. F: Approximately half of MPT cells can be seen to display strong to moderate cytoplasmic WT1 immunoreactivity. G: Some MPT cells exhibited perinuclear dot-like WT1 staining pattern. H: In contrast, normal tubal epithelium showed moderate nuclear WT1 immunoreactivity. I: Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) expression of MPT was also found to differ from that of normal tubal epithelium. J: MPT cells did not show PTEN expression. Moderate-to-weak PTEN immunoreactivity in stromal cells served as an internal positive control. K: In contrast, normal tubal epithelium showed cytoplasmic PTEN expression. L: The Ki-67 labeling index was very low (less than 1%) in MPT. M: p53 immunostaining revealed wild-type expression pattern (patchy distribution and weak intensity) in MPT. N: MPT cells were negative for human human epidermal growth factor receptor 2. Original magnification: A-C, ×40; D, ×200; E, ×40; F-G, ×200; H-J, ×100; K-L, ×200; M, ×100; N, ×200.*

Table II. *Clinical features of tubal metaplastic papillary tumor.*

Case	Year reported	Author (reference)	Age (years)	Obstetric history	Associated condition/ symptoms	Tumor marker			Surgery	Current status	Follow-up time
						CA 125 (IU/ml)	CA 19-9 (IU/ml)	CEA (ng/ml)			
1	1978	Starr *et al*. (7)	26	G2P1	Normal delivery	NA	NA	NA	Tubal ligation followed by TH and BSO	NED	3 Months
2-5	1980	Saffos *et al*. (8)	27-33	Multi-parous (4/4)	Normal delivery (4/4), previous OC medication (1/4)	NA	NA	NA	Tubal ligation followed by TH and BSO (2/4)	NED	1.5-6 Years
6	1988	Keeney and Thrasher (9)	27	G3P1A1	Cesarean delivery, hypothyroidism, PROM	NA	NA	NA	Tubal ligation	NED	4 Years
7	1989	Bartnik *et al*. (10)	23	G3P2	Respiratory and urinary tract infection during second and third trimesters	NA	NA	NA	Tubal ligation	NED	NA
8	1999	Pang (11)	52	G5P3A2	Previous tubal pregnancy, previous OC medication, low abdominal fullness	NA	NA	NA	Bilateral salpingectomy	NED	NA
9	2003	Solomon *et al*. (12)	26	G5P3A1	Previous OC medication, subchorionic bleeding, preterm labor, IUGR	NA	NA	NA	Tubal ligation	NED	6 Weeks
10	2011	D'Adda *et al*. (13)	31	NA	Cesarean delivery, podalic fetal presentation	NA	NA	NA	Left salpingectomy	NA	NA
11	2015	Salazar *et al*. (14)	41	G4	Cesarean delivery	NA	NA	NA	Tubal ligation	NED	NA
12	2017	Jang *et al*. (this study)	51	G2P2	EM cancer, vaginal bleeding	4.0	5.8	0.3	TH, BSO, and BPLND	NED	2 Years

A: Abortion, BPLND: bilateral pelvic lymph node dissection, BSO: bilateral salpingo-oophorectomy, CEA: carcinoembryonic antigen, EM: endometrium, G: gravidity, IUGR: intrauterine growth retardation, NA: not applicable, NED: no evidence of disease, OC: oral contraceptive, P: parity, PROM: premature rupture of membrane, TAH: total hysterectomy, US: ultrasonography.

cells showing distinctive abundant eosinophilic cytoplasm, intracytoplasmic and extracellular mucin, with/without mild pseudostratification. MPT is usually confined to the mucosa and does not show moderate-to-severe cytological atypia or coagulative tumor cell necrosis.

To the best of our knowledge, 12 cases of tubal MPT have been reported in the English literature (7-14). Table II summarizes the clinical features of 12 patients diagnosed with tubal MPT. Of nine tubal MPT case reports, eight were single case reports and one was a series of four cases. Ten out of the 12 tubal MPT cases were detected in intrauterine pregnancies or the postpartum period. These patients were aged 23-41 years. Of the other two cases, one was a 52-year-old patient with hydrosalpinx from a previous tubal pregnancy, and the other was a 51-year-old patient diagnosed with endometrial cancer. Three patients had a history of oral contraceptive use prior to MPT diagnosis, and one was taking L-thyroxine at the time of diagnosis. Five patients with tubal MPT had obstetric problems, such as premature rupture of membranes, respiratory and urinary tract infection during the second and third trimesters, previous tubal pregnancy, subchorionic bleeding, preterm labor, intrauterine growth retardation, and podalic fetal presentation. Except for one patient who showed bilateral hydrosalpinx by ultrasonography, no imaging studies of the fallopian tubes were performed in the other 11 cases. Although ultrasonography was performed in our case, the purpose was to examine the endometrial lesion. Apart from our case, the

other 11 cases did not include any tests for serum tumor markers. Serum levels of cancer antigen (CA) 125, CA19-9, and carcinoembryonic antigen measured in our case were all within the normal range. Among 10 patients with intrauterine pregnancy-related MPT, nine patients underwent postpartum tubal ligation. The other underwent a unilateral salpingectomy because of a small nodule detected on the tubal surface. Of the two cases unrelated to intrauterine pregnancy, one patient underwent bilateral salpingectomy to treat bilateral hydrosalpinx, and the other underwent total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection to treat endometrial cancer. Among the 11 cases with follow-up information available, there were no cases of tumor recurrence or death due to MPT. In the seven cases that mentioned the follow-up time, the observation period ranged from 6 weeks to 6 years.

Table III summarizes the pathological features of tubal MPT. There were three cases of grossly visible luminal dilatation and six cases in which a grossly identifiable lesion was absent. Two cases presented with an intraluminal exophytic lesion and mucoid material, respectively, and one case presented with a small nodule on the tubal surface. In all eight cases for which the extent of MPT was reported, it was described as a circumscribed mucosal lesion. Four cases did not mention laterality at all. Three cases each were reported in the right and left fallopian tubes, while the remaining two cases were unilateral lesions, but laterality was not reported. None of the MPT case reports involved bilateral fallopian tubes. Only three case reports described lesion size because MPT is usually microscopic and is detected incidentally. All reported cases of MPT to date were smaller than 1.0 cm, ranging from 0.2 to 0.9 cm. Histologically, a single layer or pseudostratified layer of epithelial proliferation with papillary/adenomatous configuration was consistently observed in all cases. The individual cells were non-ciliated columnar cells with abundant eosinophilic cytoplasm, and epithelial proliferation was limited to the mucosa. Most cases reported that MPT cells contained intracytoplasmic mucin. Some cases reported that MPT cells had enlarged, hyperchromatic, or vesicular nuclei with conspicuous nucleoli, but cytological atypia was minimal to mild, and severe nuclear pleomorphism was not observed. Two cases, including ours, exhibited nuclear grooves and intranuclear pseudoinclusion. Intranuclear pseudoinclusion was observed more frequently than nuclear grooves or folds in our case. We also observed occasional psammomatous microcalcification in our case.

A single mitotic figure was reported in two out of the 12 cases, and one of these cases reported an atypical (tripolar) mitotic figure. Of the 10 cases that discussed the presence or absence of extracellular mucin, extracellular mucin was observed in seven and not observed in three cases. Mucinous material in the tubal lumen and between papillae was confirmed by a mucin stain, such as periodic acid-Schiff, mucicarmine, or Alcian Blue. No evidence of coagulative tumor cell necrosis or atypical mitotic figures were observed in our case. Minimal chronic salpingitis accompanied MPT in some cases.

We analyzed the immunophenotype of tubal MPT with immunohistochemical staining for a range of markers. Firstly, loss of PTEN expression was observed in the MPT cells. PTEN is a tumor suppressor that negatively regulates the phosphatidylinositol 3-kinase-AKT signaling pathway, which is implicated in the pathogenesis of endometrial or ovarian endometrioid carcinoma (15-19). Based on the loss of PTEN protein expression in MPT cells compared to normal tubal epithelium, we surmised that PTEN loss might be involved in the pathogenesis of MPT. However, it is unreasonable to reach a firm conclusion based on the immunostaining result from a single case. It is necessary to analyze genetic or epigenetic alterations of *PTEN* in tubal MPT and conduct further investigations into the PTEN expression status in multiple MPT cases.

Secondly, we also observed a reduction in WT1 immunoreactivity in MPT cells compared to that in normal tubal epithelium. WT1 is normally expressed in the nuclei of fallopian tube epithelium. While WT1 expression was considerably reduced in MPT cell nuclei, strong to moderate WT1 expression was observed in the cytoplasm. Similarly to the changes in PTEN expression, we noted, as far as we are aware for the first time, that WT1 expression was different in MPT compared to normal tubal epithelium. Cytoplasmic WT1 expression is observed in many kinds of tumor cells. Nakatsuka *et al*. observed diffuse or granular cytoplasmic WT1 expression in carcinomas of the stomach, prostate, biliary tract, and urinary systems (20). These authors also observed extremely strong cytoplasmic WT1 staining in glioblastomas, some soft-tissue sarcomas, and cutaneous malignant melanomas compared with other tumor types. Similarly, Magro *et al*. observed cytoplasmic WT1 expression in all cases of infantile fibrosarcoma that they analyzed but did not observe WT1 expression in nodular fasciitis or desmoid-type fibromatosis (20). Based on these results, they proposed that cytoplasmic expression of WT1 was a useful immunomarker in the differential diagnosis of infantile fibrosarcoma. Niksic *et al*. observed differences in a proportion of cytoplasmic WT1 between cell types, and claimed that WT1 protein was involved in regulating translation as it shuttled between the nucleus and cytoplasm (21). Although this immunostaining result was from a single case, we consider WT1 cytoplasmic expression in MPT of the fallopian tube a novel finding that could be used as an immunomarker for this tumor entity. Further investigations are necessary to clarify the role of altered WT1 protein expression in the development of tubal MPT.

Table III. *Pathological features of tubal metaplastic papillary tumor.*

Case	Author (reference)	Gross finding	Location and extent	Size (cm)	Architectural feature	Cytological feature	Mitotic count and atypical mitotic figure	Coagulative tumor cell necrosis
1	Starr *et al*. (7)	Slight luminal dilatation	Left; confined to the mucosa	NA	Papillary configuration	Misdiagnosed as grade 1 papillary adenocarcinoma	NA, no atypical mitotic figure	NA
2-5	Saffos *et al*. (8)	No gross abnormalities	Confined to the mucosa	NA	Papillary and adenomatous configuration, small cysts deep to the papillae, single or pseudostratified cell layers, epithelial budding	Non-ciliated, columnar cells with abundant, eosinophilic cytoplasm and large pale to vesicular nuclei, prominent nucleoli, some mucin-containing cells, extracellular mucin	1 (1/4), 0 (3/4), no atypical mitotic figure	NA
6	Keeney and Thrasher (9)	No gross abnormalities	Unilateral; confined to the mucosa	NA	Papillary and adenomatous configuration, glandular and papillary proliferation with one to two cell layers	Non-ciliated, columnar cells with abundant acidophlilic cytoplasm and large vesicular nuclei, mucin-containing cells	1 (1/4; tripolar mitosis)	NA
7	Bartnik *et al*. (10)	Intraluminal pale yellow, mucoid material	Right; confined to the mucosa	NA	Papillary configuration predominantly single or pseudostratified cell layers	Oxyphilic columnar cells and mucin-containing cells with basal nuclei, extracellular mucin	0	NA
8	Pang (11)	Luminal dilatation	Right	NA	Papillary configuration one to two cell layers, edematous stroma	Non-ciliated, columnar cells with eosinophilic cytoplasm, a few mucin-containing cells, extracellular mucin	NA	NA
9	Solomon *et al*. (12)	No gross abnormalities	Left	0.2	Papillary configuration, single cell layer with occasional pseudo-stratification	Simple columnar cells with abundant eosinophilic cytoplasm, elongated vesicular nuclei, some mucin- containing cells, extravasation of mucin	0	NA
10	D'Adda *et al*. (13)	Small nodule on the tubal surface	Left	0.9	Papillary configuration, epithelial budding	Abundant, eosinophilic cytoplasm with slight nuclear pleomorphism	0	NA
11	Salazar *et al*. (14)	Luminal dilatation with caramel-like substances	Unilateral	NA	Branching papillae, epithelial budding and pseudo-stratification	Non-ciliated, columnar cells with plump, eosinophilic cytoplasm, enlarged nuclei with prominent nucleoli, nuclear pseudoinclusion, groove, mucin-containing cells with occasional cyst-like change, extracellular mucin	0	NA
12	Jang *et al*. (this study)	Intraluminal exophytic, papillary lesion	Right; confined to the mucosa	0.5	Papillary configuration, single cell layer with pseudo-stratification, floating papillary tuft, myxoid stroma	Non-ciliated, columnar cells with plump, eosinophilic cytoplasm and slight nuclear pleomorphism, pseudoinclusion and groove in few area, extracellular mucin, psammomatous microcalcification, intracytoplasmic basophilic granules, apical cytoplasmic blebs or snouts in occasional	0	Absent

NA: Not applicable.

In summary, we described the clinicopathological characteristics of a tubal MPT case. We provided a thorough review of previously published case reports and described an additional case of tubal MPT. MPT of the fallopian tube exhibits distinctive histopathological features and immunophenotype. Due to its rarity, very little information is available on the clinicopathological characteristics of tubal MPT. We demonstrated for the first time loss of PTEN expression and cytoplasmic WT1 immunoreactivity in tubal MPT, novel findings that could be used as immunomarkers for this tumor type. Further investigation using a large cohort is necessary to establish the biological nature and pathogenetic mechanism of tubal MPT.

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